THE CONCISE GUIDE TO PHARMACOLOGY 2019/20

THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: Enzymes

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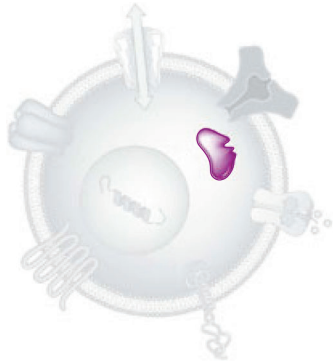

Abstract

The Concise Guide to PHARMACOLOGY 2019/20 is the fourth in this series of biennial publications. The Concise Guide provides concise overviews of the key properties of nearly 1800 human drug targets with an emphasis on selective pharmacology (where available), plus links to the open access knowledgebase source of drug targets and their ligands (www.guidetopharmacology.org), which provides more detailed views of target and ligand properties. Although the Concise Guide represents approximately 400 pages, the material presented is substantially reduced compared to information and links presented on the website. It provides a permanent, citable, point-in-time record that will survive database updates. The full contents of this section can be found at http://onlinelibrary.wiley.com/doi/10.1111/bph.14752. Enzymes are one of the six major pharmacological targets into which the Guide is divided, with the others being: G protein-coupled receptors, ion channels, nuclear hormone receptors, catalytic receptors and transporters. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading. The landscape format of the Concise Guide is designed to facilitate comparison of related targets from material contemporary to mid-2019, and supersedes data presented in the 2017/18, 2015/16 and 2013/14 Concise Guides and previous Guides to Receptors and Channels. It is produced in close conjunction with the International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR), therefore, providing official IUPHAR classification and nomenclature for human drug targets, where appropriate.

Conflict of interest

The authors state that there are no conflicts of interest to disclose.

Overview: Enzymes are protein catalysts facilitating the conversion of substrates into products. The Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB) classifies enzymes into families, using a four number code, on the basis of the reactions they catalyse. There are six main families:
EC 1.-.-.- Oxidoreductases;
EC 2.-.-.- Transferases;
EC 3.-.-.- Hydrolases;
EC 4.-.-.- Lyases;
EC 5.-.-.- Isomerases;
EC 6.-.-.- Ligases.
Although there are many more enzymes than receptors in biology, and many drugs that target prokaryotic enzymes are effective medicines, overall the number of enzyme drug targets is relatively small [454, 492], which is not to say that they are of modest importance.
The majority of drugs which act on enzymes act as inhibitors; one exception is metformin, which appears to stimulate activity of AMP-activated protein kinase, albeit through an imprecisely-defined mechanism. Kinetic assays allow discrimination of competitive, non-competitive, and un-competitive inhibitors. The majority of inhibitors are competitive (acting at the enzyme's ligand recognition site), non-competitive (acting at a distinct site; potentially interfering with co-factor or co-enzyme binding) or of mixed type. One rare example of an uncompetitive inhibitor is lithium ions, which are effective inhibitors at inositol monophosphatase only in the presence of high substrate concentrations. Some inhibitors are irreversible, including a group known as suicide substrates, which bind to the ligand recognition site and then

couple covalently to the enzyme. It is beyond the scope of the Guide to give mechanistic information about the inhibitors described, although generally this information is available from the indicated literature.

Many enzymes require additional entities for functional activity. Some of these are used in the catalytic steps, while others promote a particular conformational change. Co-factors are tightly bound to the enzyme and include metal ions and heme groups. Co-enzymes are typically small molecules which accept or donate functional groups to assist in the enzymatic reaction. Examples include ATP, NAD, NADP and S-adenosylmethionine, as well as a number of vitamins, such as riboflavin (vitamin B1) and thiamine (vitamin B2). Where co-factors/co-enzymes have been identified, the Guide indicates their involvement.

Family structure

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- S319 Chromatin modifying enzymes
- 1.14.11.- Histone demethylases
- S319 2.1.1.- Protein arginine N-methyltransferases
- 2.1.1.43 Histone methyltransferases (HMTs)
- 2.3.1.48 Histone acetyltransferases (HATs)
- S320 3.5.1.- Histone deacetylases (HDACs)
- 3.6.1.3 ATPases
- Enzymatic bromodomain-containing proteins
- Bromodomain kinase (BRDK) family
- TAF1 family
- TIF1 family
- S321 Cyclic nucleotide turnover/signalling
- S321 Adenylyl cyclases (ACs)
- S323 Exchange protein activated by cyclic AMP (EPACs)
- S323 Phosphodiesterases, 3′,5′-cyclic nucleotide (PDEs)
- S327 Cytochrome P450
- S327 CYP1 family
- S328 CYP2 family
- S329 CYP3 family
- S330 CYP4 family
- S331 CYP5, CYP7 and CYP8 families
- S332 CYP11, CYP17, CYP19, CYP20 and CYP21 families
- S333 CYP24, CYP26 and CYP27 families
- S333 CYP39, CYP46 and CYP51 families
- DNA glycosylases
- S334 DNA topoisomerases
- S335 Endocannabinoid turnover
- S336 *N*-Acylethanolamine turnover
- S337 2-Acylglycerol ester turnover
- S338 Eicosanoid turnover
- S338 Cyclooxygenase
- S339 Prostaglandin synthases
- S341 Lipoxygenases
- S342 Leukotriene and lipoxin metabolism
- S343 GABA turnover
- S344 Glycerophospholipid turnover
- S344 Phosphoinositide-specific phospholipase C
- S346 Phospholipase A_2
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- S349 Lipid phosphate phosphatases
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- S352 1-phosphatidylinositol-3-phosphate 5-kinase family
- S353 Type I PIP kinases (1-phosphatidylinositol-4-phosphate 5-kinase family)
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- S354 Sphingosine kinase
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- S358 Hydrogen sulphide synthesis
- S358 Hydrolases
- S360 Inositol phosphate turnover
- S360 Inositol 1,4,5-trisphosphate 3-kinases
- S360 Inositol polyphosphate phosphatases
- S361 Inositol monophosphatase
- Itaconate biosynthesis
- S361 Kinases (EC 2.7.x.x)
- AGC: Containing PKA, PKG, PKC families
- DMPK family
- GEK subfamily
- Other DMPK family kinases
- S362 Rho kinase
- G protein-coupled receptor kinases (GRKs)
- Beta-adrenergic receptor kinases (βARKs)
- Opsin/rhodopsin kinases
- GRK4 subfamily
- MAST family
- NDR family
- PDK1 family
- Protein kinase A (PKA) family
- Akt (Protein kinase B, PKB) family
- S362 Protein kinase C (PKC) family
- S363 Alpha subfamily
- S363 Delta subfamily
- S364 Eta subfamily
- Iota subfamily
- Protein kinase G (PKG) family
- Protein kinase N (PKN) family
- RSK family
- MSK subfamily
- p70 subfamily
- RSK subfamily
- RSKR subfamily
- RSKL family
- SGK family
- YANK family
- Atypical
- ABC1 family

Acetylcholine turnover

Enzymes → Acetylcholine turnover

Overview: Acetylcholine is familiar as a neurotransmitter in the central nervous system and in the periphery. In the somatic nervous system, it activates nicotinic acetylcholine receptors at the skeletal neuromuscular junction. It is also employed in the autonomic nervous system, in both parasympathetic and sympathetic branches; in the former, at the smooth muscle neuromuscular junction, activating muscarinic acetylcholine receptors. In the latter, acetylcholine is involved as a neurotransmitter at the ganglion, activating nicotinic acetylcholine receptors. Acetylcholine is synthesised in neurones through the action of choline O-acetyltransferase and metabolised after release through the extracellular action of acetylcholinesterase and cholinesterase. Choline is accumulated from the extracellular medium by selective transporters (see SLC5A7 and the SLC44 family). Acetylcholine is accumulated in synaptic vesicles through the action of the vesicular acetylcholine transporter SLC18A3.

Nomenclature	choline O-acetyltransferase	acetylcholinesterase (Cartwright blood group)	butyrylcholinesterase
Common abbreviation	ChAT	AChE	BChE
HGNC, UniProt	*CHAT*, P28329	*ACHE*, P22303	*BCHE*, P06276
EC number	2.3.1.6: acetyl CoA + choline = acetylcholine + coenzyme A	3.1.1.7: acetylcholine + H_2O = acetic acid + choline + H^+	3.1.1.7: acetylcholine + H_2O = acetic acid + choline + H^+
Inhibitors	compound 2 (pIC_{50} 6.5) [216] – Mouse	tacrine (pK_i 7.5) [67], galantamine (pIC_{50} 6.3) [108], rivastigmine (pIC_{50} 5.4) [380]	rivastigmine (pIC_{50} 7.4) [380], tacrine (pK_i 7.2) [67]
Sub/family-selective inhibitors	–	physostigmine (pIC_{50} 7.6–7.8) [380]	physostigmine (pIC_{50} 7.6–7.8) [380]
Selective inhibitors	–	donepezil (pIC_{50} 7.7–8.3) [78, 193, 380], BW284C51 (pIC_{50} 7.7) [205]	bambuterol (pIC_{50} 8.5) [205]
Comments	Splice variants of choline O-acetyltransferase are suggested to be differentially distributed in the periphery and CNS (see [40]).	–	–

Comments: A number of organophosphorus compounds inhibit acetylcholinesterase and cholinesterase irreversibly, including pesticides such as chlorpyrifos-oxon, and nerve agents such as tabun, soman and sarin. AChE is unusual in its exceptionally high turnover rate which has been calculated at 740 000/min/molecule [644].

Further reading on Acetylcholine turnover

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Masson P *et al.* (2016) Slow-binding inhibition of cholinesterases, pharmacological and toxicological relevance. *Arch Biochem Biophys* **593**: 60-8 [PMID:26874196]

Rotundo RL. (2017) Biogenesis, assembly and trafficking of acetylcholinesterase. *J Neurochem* **142 Suppl 2**: 52-58 [PMID:28326552]

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Adenosine turnover

Enzymes → Adenosine turnover

Overview: A multifunctional, ubiquitous molecule, adenosine acts at cell-surface G protein-coupled receptors, as well as numerous enzymes, including protein kinases and adenylyl cyclase. Extracellular adenosine is thought to be produced either by export or by metabolism, predominantly through ecto-5′-nucleotidase activity (also producing inorganic phosphate). It is inactivated either by extracellular metabolism *via* adenosine deaminase (also producing ammonia) or, following uptake by nucleoside transporters, *via* adenosine deaminase or adenosine kinase (requiring ATP as co-substrate). Intracellular adenosine may be produced by cytosolic 5′-nucleotidases or through S-adenosylhomocysteine hydrolase (also producing L-homocysteine).

Nomenclature	Adenosine deaminase	Adenosine kinase	Ecto-5′-Nucleotidase	S-Adenosylhomocysteine hydrolase
Systematic nomenclature	–	–	CD73	–
Common abbreviation	ADA	ADK	NT5E	SAHH
HGNC, UniProt	*ADA*, P00813	*ADK*, P55263	*NT5E*, P21589	*AHCY*, P23526
EC number	3.5.4.4: adenosine + H_2O = inosine + NH_3	2.7.1.20	3.1.3.5	3.3.1.1
Rank order of affinity	2′-deoxyadenosine > adenosine	adenosine	adenosine 5′-monophosphate, 5′-GMP, 5′-inosine monophosphate, 5′-UMP > 5′-dAMP, 5′-dGMP	–
Endogenous substrates	–	–	–	S-adenosylhomocysteine
Products	2′-deoxyinosine, inosine	adenosine 5′-monophosphate	uridine, inosine, guanine, adenosine	adenosine
Inhibitors	–	–	–	DZNep (pK_i 12.3) [208] – Hamster
Selective inhibitors	pentostatin (pIC_{50} 10.8) [6], EHNA (pK_i 8.8) [6]	A134974 (pIC_{50} 10.2) [403], ABT702 (pIC_{50} 8.8) [287]	αβ-methyleneADP (pIC_{50} 8.7) [65]	3-deazaadenosine (pIC_{50} 8.5) [227]
Comments	–	The enzyme exists in two isoforms derived from alternative splicing of a single gene product: a short isoform, ADK-S, located in the cytoplasm is responsible for the regulation of intra- and extracellular levels of adenosine and hence adenosine receptor activation; a long isoform, ADK-L, located in the nucleus contributes to the regulation of DNA methylation [57, 642].	Pharmacological inhibition of CD73 is being investigated as a novel cancer immunotherapy strategy [622].	–

Comments: An extracellular adenosine deaminase activity, termed ADA2 or adenosine deaminase growth factor (ADGF, *CECR1*, Q9NZK5) has been identified [117, 387], which is insensitive to EHNA [671]. Other forms of adenosine deaminase act on ribonucleic acids and may be divided into two families: *ADAT1* (Q9BUB4) deaminates transfer RNA; *ADAR* (EC 3.5.4.37, also known as 136 kDa double-stranded RNA-binding protein, P136, K88DSRBP, Interferon-inducible protein 4); *ADARB1* (EC 3.5.-.-, , also known as dsRNA adenosine deaminase) and *ADARB2* (EC 3.5.-.-, also known as dsRNA adenosine deaminase B2, RNA-dependent adenosine deaminase 3) act on double-stranded RNA. Particular polymorphisms of the ADA gene result in loss-of-function and severe combined immunodeficiency syndrome. Adenosine deaminase is able to complex with dipeptidyl peptidase IV (EC 3.4.14.5, *DPP4*, also known as T-cell activation antigen CD26, TP103, adenosine deaminase complexing protein 2) to form a cell-surface activity [301].

Further reading on Adenosine turnover

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Xiao Y *et al.* (2015) Role of S-adenosylhomocysteine in cardiovascular disease and its potential epigenetic mechanism. *Int. J. Biochem. Cell Biol.* **67**: 158-66 [PMID:26117455]

Amino acid hydroxylases

Enzymes → Amino acid hydroxylases

Overview: The amino acid hydroxylases (monooxygenases), EC.1.14.16.-, are iron-containing enzymes which utilise molecular oxygen and sapropterin as co-substrate and co-factor, respectively. In humans, as well as in other mammals, there are two distinct L-Tryptophan hydroxylase 2 genes. In humans, these genes are located on chromosomes 11 and 12 and encode two different homologous enzymes, TPH1 and TPH2.

Nomenclature	L-Phenylalanine hydroxylase	L-Tyrosine hydroxylase	L-Tryptophan hydroxylase 1	L-Tryptophan hydroxylase 2
HGNC, UniProt	*PAH*, P00439	*TH*, P07101	*TPH1*, P17752	*TPH2*, Q8IWU9
EC number	1.14.16.1: L-phenylalanine + O_2 -> L-tyrosine	1.14.16.2: L-tyrosine + O_2 -> levodopa	1.14.16.4	1.14.16.4
Endogenous substrates	L-phenylalanine	L-tyrosine	L-tryptophan	L-tryptophan
Products	L-tyrosine	levodopa	5-hydroxy-L-tryptophan	5-hydroxy-L-tryptophan
Cofactors	sapropterin	sapropterin, Fe^{2+}	–	–
Endogenous activators	Protein kinase A-mediated phosphorylation (Rat) [2]	Protein kinase A-mediated phosphorylation [290]	Protein kinase A-mediated phosphorylation [291]	Protein kinase A-mediated phosphorylation [291]
Inhibitors	–	–	telotristat ethyl [311]	–
Selective inhibitors	α-methylphenylalanine [218] – Rat, fenclonine	α-propyldopacetamide, 3-chlorotyrosine, 3-iodotyrosine, alpha-methyltyrosine	α-propyldopacetamide, 6-fluorotryptophan [434], fenclonine, fenfluramine	α-propyldopacetamide, 6-fluorotryptophan [434], fenclonine, fenfluramine
Comments	PAH is an iron bound homodimer or -tetramer from the same structural family as tyrosine 3-monooxygenase and the tryptophan hydroxylases. Deficiency or loss-of-function of PAH is associated with phenylketonuria	TH is a homotetramer, which is inhibited by dopamine and other catecholamines in a physiological negative feedback pathway [127].	–	–

Further reading on Amino acid hydroxylases

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L-Arginine turnover

Enzymes → L-Arginine turnover

Overview: L-arginine is a basic amino acid with a guanidino sidechain. As an amino acid, metabolism of L-arginine to form L-ornithine, catalysed by arginase, forms the last step of the urea production cycle. L-Ornithine may be utilised as a precursor of polyamines (see Carboxylases and Decarboxylases) or recycled via L-argininosuccinic acid to L-arginine. L-Arginine may itself be decarboxylated to form agmatine, although the prominence of this pathway in human tissues is uncertain. L-Arginine may be used as a precursor for guanidoacetic acid formation in the creatine synthesis pathway under the influence of arginine:glycine amidinotransferase with L-ornithine as a byproduct. Nitric oxide synthase uses L-arginine to generate nitric oxide, with L-citrulline also as a byproduct.
L-Arginine in proteins may be subject to post-translational modification through methylation, catalysed by protein arginine methyltransferases. Subsequent proteolysis can liberate asymmetric N^G,N^G-dimethyl-L-arginine (ADMA), which is an endogenous inhibitor of nitric oxide synthase activities. ADMA is hydrolysed by dimethylarginine dimethylhydrolase activities to generate L-citrulline and dimethylamine.

2.1.1.- Protein arginine N-methyltransferases

Enzymes → L-Arginine turnover → 2.1.1.- Protein arginine N-methyltransferases

Overview: Protein arginine *N*-methyltransferases (PRMT, EC 2.1.1.-) encompass histone arginine *N*-methyltransferases (PRMT4, PRMT7, EC 2.1.1.125) and myelin basic protein *N*-methyltransferases (PRMT7, EC 2.1.1.126). They are dimeric or tetrameric enzymes which use S-adenosyl methionine as a methyl donor, generating S-adenosylhomocysteine as a by-product. They generate both mono-methylated and di-methylated products; these may be symmetric (SDMA) or asymmetric (N^G,N^G-dimethyl-L-arginine) versions, where both guanidine nitrogens are monomethylated or one of the two is dimethylated, respectively.

Information on members of this family may be found in the online database.

Arginase

Enzymes → L-Arginine turnover → Arginase

Overview: Arginase (EC 3.5.3.1) are manganese-containing isoforms, which appear to show differential distribution, where the ARG1 isoform predominates in the liver and erythrocytes, while ARG2 is associated more with the kidney.

Information on members of this family may be found in the online database.

Comments: N^{ω}-hydroxyarginine, an intermediate in NOS metabolism of L-arginine acts as a weak inhibitor and may function as a physiological regulator of arginase activity. Although isoform-selective inhibitors of arginase are not available, examples of inhibitors selective for arginase compared to NOS are N^{ω}-hydroxy-nor-L-arginine [592], S-(2-boronoethyl)-L-cysteine [111, 312] and 2(*S*)-amino-6-boronohexanoic acid [32, 111].

Arginine:glycine amidinotransferase

Enzymes → L-Arginine turnover → Arginine:glycine amidinotransferase

Nomenclature	Arginine:glycine amidinotransferase
Common abbreviation	AGAT
HGNC, UniProt	*GATM*, P50440
EC number	2.1.4.1

Dimethylarginine dimethylaminohydrolases

Enzymes → L-Arginine turnover → Dimethylarginine dimethylaminohydrolases

Overview: Dimethylarginine dimethylaminohydrolases (DDAH, EC 3.5.3.18) are cytoplasmic enzymes which hydrolyse N^{G},N^{G}-dimethyl-L-arginine to form dimethylamine and L-citrulline.

Nomenclature	N^{G},N^{G}-Dimethylarginine dimethylaminohydrolase 1	N^{G},N^{G}-Dimethylarginine dimethylaminohydrolase 2
Common abbreviation	DDAH1	DDAH2
HGNC, UniProt	*DDAH1*, O94760	*DDAH2*, O95865
EC number	3.5.3.18	3.5.3.18
Cofactors	Zn^{2+}	–
Inhibitors	compound 2e (pK_i 5.7) [324]	–

Nitric oxide synthases

Enzymes → L-Arginine turnover → Nitric oxide synthases

Overview: Nitric oxide synthases (NOS, E.C. 1.14.13.39) are a family of oxidoreductases that synthesize nitric oxide (NO.) via the NADPH and oxygen-dependent consumption of L-arginine with the resultant by-product, L-citrulline. There are 3 NOS isoforms and they are related by their capacity to produce NO, highly conserved organization of functional domains and significant homology at the amino acid level. NOS isoforms are functionally distinguished by the cell type where they are expressed, intracellular targeting and transcriptional and post-translation mechanisms regulating enzyme activity. The nomenclature suggested by **NC-IUPHAR** of NOS I, II and III [420] has not gained wide acceptance, and the 3 isoforms are more commonly referred to as neuronal NOS (nNOS), inducible NOS (iNOS) and endothelial NOS (eNOS) which reflect the location of expression (nNOS and eNOS) and inducible expression (iNOS). All are dimeric enzymes that shuttle electrons from NADPH, which binds to a C-terminal reductase domain, through the flavins FAD and FMN to the oxygenase domain of the other monomer to enable the BH4-dependent reduction of heme bound oxygen for insertion into the substrate, L-arginine. Electron flow from reductase to oxygenase domain is controlled by calmodulin binding to canonical calmodulin binding motif located between these domains. eNOS and nNOS isoforms are activated at concentrations of calcium greater than 100 nM, while iNOS shows higher affinity for Ca^{2+}/calmodulin (*CALM1 CALM2 CALM3*, P62158) with great avidity and is essentially calcium-independent and constitutively active. Efficient stimulus-dependent coupling of nNOS and eNOS is achieved *via* subcellular targeting through respective N-terminal PDZ and fatty acid acylation domains whereas iNOS is largely cytosolic and function is independent of intracellular location. nNOS is primarily expressed in the brain and neuronal tissue, iNOS in immune cells such as macrophages and eNOS in the endothelial layer of the vasculature although exceptions in other cells have been documented. L-NAME and related modified arginine analogues are inhibitors of all three isoforms, with IC_{50} values in the micromolar range.

Nomenclature	Endothelial NOS	Inducible NOS	Neuronal NOS
Common abbreviation	eNOS	iNOS	nNOS
HGNC, UniProt	*NOS3*, P29474	*NOS2*, P35228	*NOS1*, P29475
EC number	1.14.13.39	1.14.13.39	1.14.13.39
Endogenous Substrate	L-arginine	L-arginine	L-arginine
Products	NO, L-citrulline	NO, L-citrulline	L-citrulline, NO
Cofactors	oxygen, BH4, Zn^{2+}, flavin mononucleotide, NADPH, heme, flavin adenine dinucleotide	heme, flavin mononucleotide, flavin adenine dinucleotide, oxygen, NADPH, Zn^{2+}, BH4	flavin adenine dinucleotide, heme, oxygen, BH4, flavin mononucleotide, NADPH, Zn^{2+}
Selective inhibitors	–	1400W (pIC_{50} 8.2) [201], 2-amino-4-methylpyridine (pIC_{50} 7.4) [164], PIBTU (pIC_{50} 7.3) [202], NIL (pIC_{50} 5.5) [421], aminoguanidine [115]	3-bromo-7NI (pIC_{50} 6.1–6.5) [52], 7NI (pIC_{50} 5.3) [24]

Comments: The reductase domain of NOS catalyses the reduction of cytochrome c and other redox-active dyes [400]. NADPH:O_2 oxidoreductase catalyses the formation of superoxide anion/H_2O_2 in the absence of L-arginine and sapropterin.

Further reading on Nitric oxide synthases

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Further reading on L-Arginine turnover

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Carbonic anhydrases

Enzymes → Carbonic anhydrases

Overview: Carbonic anhydrases facilitate the interconversion of water and carbon dioxide with bicarbonate ions and protons (EC 4.2.1.1), with over a dozen gene products identified in man. The enzymes function in acid-base balance and the movement of carbon dioxide and water. They are targetted for therapeutic gain by particular antiglaucoma agents and diuretics.

Nomenclature	carbonic anhydrase 1	carbonic anhydrase 7	carbonic anhydrase 12	carbonic anhydrase 13	carbonic anhydrase 14
Common abbreviation	CA I	CA VII	CA XII	CA XIII	CA XIV
HGNC, UniProt	*CA1*, P00915	*CA7*, P43166	*CA12*, O43570	*CA13*, Q8N1Q1	*CA14*, Q9ULX7
EC number	4.2.1.1	4.2.1.1	4.2.1.1	4.2.1.1	4.2.1.1
Inhibitors	chlorthalidone (pK_i 6.5)	methazolamide (pK_i 8.7) [533], acetazolamide (pK_i 8.6) [23], brinzolamide (pK_i 8.6) [533], chlorthalidone (pK_i 8.6) [591]	SLC-0111 (pK_i 8.4) [112]	–	–

Further reading on Carbonic anhydrases

Imtaiyaz Hassan M, Shajee B, Waheed A, Ahmad F and Sly WS. (2013) Structure, function and applications of carbonic anhydrase isozymes. *Bioorg Med Chem* **21**: 1570-70 [PMID:22607884]
Supuran CT (2017) Advances in structure-based drug discovery of carbonic anhydrase inhibitors. *Expert Opin Drug Discov* **12**: 61-88 [PMID:27783541]
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Carboxylases and decarboxylases

Enzymes → Carboxylases and decarboxylases

Carboxylases

Enzymes → Carboxylases and decarboxylases → Carboxylases

Overview: The carboxylases allow the production of new carbon-carbon bonds by introducing HCO_3^- or CO_2 into target molecules. Two groups of carboxylase activities, some of which are bidirectional, can be defined on the basis of the cofactor requirement, making use of biotin (EC 6.4.1.-) or vitamin K hydroquinone (EC 4.1.1.-).

Nomenclature	Pyruvate carboxylase	Acetyl-CoA carboxylase 1	Acetyl-CoA carboxylase 2	Propionyl-CoA carboxylase	γ-Glutamyl carboxylase
Common abbreviation	PC	ACC1	ACC2	PCCA,PCCB	GGCX
HGNC, UniProt	*PC*, P11498	*ACACA*, Q13085	*ACACB*, O00763	–	*GGCX*, P38435
Subunits	–	–	–	Propionyl-CoA carboxylase β subunit, Propionyl-CoA carboxylase α subunit	–
EC number	6.4.1.1	6.4.1.2	6.4.1.2	6.4.1.3	4.1.1.90
Endogenous substrates	ATP, pyruvic acid	ATP, acetyl CoA	acetyl CoA, ATP	propionyl-CoA, ATP	glutamyl peptides
Products	P_i, ADP, oxalacetic acid	P_i, ADP, malonyl-CoA	P_i, ADP, malonyl-CoA	ADP, methylmalonyl-CoA, P_i	carboxyglutamyl peptides
Cofactors	biotin	biotin	biotin	biotin	vitamin K hydroquinone, NADPH
Inhibitors	–	–	–	–	anisindione
Selective inhibitors	–	compound 21 (pIC_{50} 8) [219], TOFA (pIC_{50} 4.9) [676]	compound 21 (pIC_{50} 8.4) [219], TOFA (pIC_{50} 4.9) [676]	–	–
Comments	–	Citrate and other dicarboxylic acids are allosteric activators of acetyl-CoA carboxylase.	Citrate and other dicarboxylic acids are allosteric activators of acetyl-CoA carboxylase.	Propionyl-CoA carboxylase is able to function in both forward and reverse activity modes, as a ligase (carboxylase) or lyase (decarboxylase), respectively.	Loss-of-function mutations in γ-glutamyl carboxylase are associated with clotting disorders.

Comments: Dicarboxylic acids including citric acid are able to activate ACC1/ACC2 activity allosterically. PCC is able to function in forward and reverse modes as a ligase (carboxylase) or lyase (decarboxylase) activity, respectively. Loss-of-function mutations in GGCX are associated with clotting disorders.

Decarboxylases

Enzymes → Carboxylases and decarboxylases → Decarboxylases

Overview: The decarboxylases generate CO_2 and the indicated products from acidic substrates, requiring pyridoxal 5-phosphate or pyruvic acid as a co-factor.

Nomenclature	Glutamic acid decarboxylase 1	Glutamic acid decarboxylase 2	Histidine decarboxylase
Common abbreviation	GAD1	GAD2	HDC
HGNC, UniProt	*GAD1*, Q99259	*GAD2*, Q05329	*HDC*, P19113
EC number	4.1.1.15: L-glutamic acid + H^+ -> GABA + CO_2	4.1.1.15: L-glutamic acid + H^+ -> GABA + CO_2	4.1.1.22
Endogenous substrates	L-glutamic acid, L-aspartic acid	L-glutamic acid, L-aspartic acid	L-histidine
Products	GABA	GABA	histamine
Cofactors	pyridoxal 5-phosphate	pyridoxal 5-phosphate	pyridoxal 5-phosphate
Selective inhibitors	s-allylglycine	s-allylglycine	AMA, FMH [198]
Comments	L-aspartic acid is a less rapidly metabolised substrate of mouse brain glutamic acid decarboxylase generating β-alanine [650]. Autoantibodies against GAD1 and GAD2 are elevated in type 1 diabetes mellitus and neurological disorders (see Further reading).		–

Nomenclature	L-Arginine decarboxylase	L-Aromatic amino-acid decarboxylase	Malonyl-CoA decarboxylase	Ornithine decarboxylase	Phosphatidylserine decarboxylase	S-Adenosylmethionine decarboxylase
Common abbreviation	ADC	AADC	MLYCD	ODC	PSDC	SAMDC
HGNC, UniProt	*AZIN2*, Q96A70	*DDC*, P20711	*MLYCD*, O95822	*ODC1*, P11926	*PISD*, Q9UG56	*AMD1*, P17707
EC number	4.1.1.19	4.1.1.28: levodopa -> dopamine + CO_2 5-hydroxy-L-tryptophan -> 5-hydroxytryptamine + CO_2 This enzyme also catalyses the following reaction:: L-tryptophan -> tryptamine + CO_2	4.1.1.9	4.1.1.17	4.1.1.65	4.1.1.50
Endogenous substrates	L-arginine	levodopa, 5-hydroxy-L-tryptophan, L-tryptophan	malonyl-CoA	L-ornithine	phosphatidylserine	S-adenosyl methionine
Products	agmatine [678]	5-hydroxytryptamine, dopamine	acetyl CoA	putrescine	phosphatidylethanolamine	S-adenosyl-L-methioninamine
Cofactors	pyridoxal 5-phosphate	pyridoxal 5-phosphate	pyridoxal 5-phosphate	pyridoxal 5-phosphate	pyruvic acid	pyruvic acid
Selective inhibitors	–	3-hydroxybenzylhydrazine, L-α-methyldopa, benserazide [125], carbidopa	–	APA (pIC_{50} 7.5) [563], eflornithine (pK_d 4.9) [482]	–	sardomozide (pIC_{50} 8) [562]
Comments	The presence of a functional ADC activity in human tissues has been questioned [110].	AADC is a homodimer.	Inhibited by AMP-activated protein kinase-evoked phosphorylation [515]	The activity of ODC is regulated by the presence of an antizyme (ENSG00000104904) and an ODC antizyme inhibitor (ENSG00000155096).	S-allylglycine is also an inhibitor of SAMDC [455].	S-allylglycine is also an inhibitor of SAMDC [455].

Further reading on Carboxylases and decarboxylases

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Catecholamine turnover

Enzymes → Catecholamine turnover

Overview: Catecholamines are defined by the presence of two adjacent hydroxyls on a benzene ring with a sidechain containing an amine. The predominant catacholamines in mammalian biology are the neurotransmitter/hormones dopamine, (-)-noradrenaline (norepinephrine) and (-)-adrenaline (epinephrine). These hormone/transmitters are synthesized by sequential metabolism from L-phenylalanine via L-tyrosine. Hydroxylation of L-tyrosine generates levodopa, which is decarboxylated to form dopamine. Hydroxylation of the ethylamine sidechain generates (-)-noradrenaline (norepinephrine), which can be methylated to form (-)-adrenaline (epinephrine). In particular neuronal and adrenal chromaffin cells, the catecholamines dopamine, (-)-noradrenaline and (-)-adrenaline are accumulated into vesicles under the influence of the vesicular monoamine transporters (VMAT1/SLC18A1 and VMAT2/SLC18A2). After release into the synapse or the bloodstream, catecholamines are accumulated through the action cell-surface transporters, primarily the dopamine (DAT/SLC6A3) and norepinephrine transporter (NET/SLC6A2). The primary routes of metabolism of these catecholamines are oxidation via monoamine oxidase activities of methylation via catechol O-methyltransferase.

Nomenclature	L-Phenylalanine hydroxylase	Tyrosine aminotransferase	L-Tyrosine hydroxylase	Dopamine beta-hydroxylase (dopamine beta-monooxygenase)
Common abbreviation	–	TAT	–	DBH
HGNC, UniProt	*PAH*, P00439	*TAT*, P17735	*TH*, P07101	*DBH*, P09172
EC number	1.14.16.1: L-phenylalanine + O_2 -> L-tyrosine	2.6.1.5: L-tyrosine + α-ketoglutaric acid -> 4-hydroxyphenylpyruvic acid + L-glutamic acid	1.14.16.2: L-tyrosine + O_2 -> levodopa	1.14.17.1: dopamine + O_2 = (-)-noradrenaline + H_2O
Endogenous substrates	L-phenylalanine	–	L-tyrosine	–
Products	L-tyrosine	–	levodopa	–
Cofactors	sapropterin	pyridoxal 5-phosphate	sapropterin, Fe^{2+}	Cu^{2+}, L-ascorbic acid
Endogenous activators	Protein kinase A-mediated phosphorylation (Rat) [2]	–	Protein kinase A-mediated phosphorylation [290]	–
Selective inhibitors	α-methylphenylalanine [218] – Rat, fenclonine	–	α-propyldopacetamide, 3-chlorotyrosine, 3-iodotyrosine, alpha-methyltyrosine	nepicastat (pIC_{50} 8) [565]
Comments	PAH is an iron bound homodimer or -tetramer from the same structural family as tyrosine 3-monooxygenase and the tryptophan hydroxylases. Deficiency or loss-of-function of PAH is associated with phenylketonuria	Tyrosine may also be metabolized in the liver by tyrosine transaminase to generate 4-hydroxyphenylpyruvic acid, which can be further metabolized to homogentisic acid. TAT is a homodimer, where loss-of-function mutations are associated with type II tyrosinemia.	TH is a homotetramer, which is inhibited by dopamine and other catecholamines in a physiological negative feedback pathway [128].	DBH is a homotetramer. A protein structurally-related to DBH (*MOXD1*, Q6UVY6) has been described and for which a function has yet to be identified [87].

Nomenclature	L-Aromatic amino-acid decarboxylase	Phenylethanolamine N-methyltransferase	Catechol-O-methyltransferase
Common abbreviation	AADC	PNMT	COMT
HGNC, UniProt	*DDC*, P20711	*PNMT*, P11086	*COMT*, P21964
EC number	4.1.1.28: levodopa -> dopamine + CO_2 5-hydroxy-L-tryptophan -> 5-hydroxytryptamine + CO_2 This enzyme also catalyses the following reaction:: L-tryptophan -> tryptamine + CO_2	2.1.1.28: (-)-noradrenaline -> (-)-adrenaline	2.1.1.6: S-adenosyl-L-methionine + a catechol = S-adenosyl-L-homocysteine + a guaiacol (-)-noradrenaline -> normetanephrine dopamine -> 3-methoxytyramine 3,4-dihydroxymandelic acid -> vanillylmandelic acid (-)-adrenaline -> metanephrine
Endogenous substrates	levodopa, 5-hydroxy-L-tryptophan, L-tryptophan	–	S-adenosyl methionine
Products	5-hydroxytryptamine, dopamine	–	tolcapone (soluble enzyme) (pK_i 9.6) [370], tolcapone (membrane-bound enzyme) (pK_i 9.5) [370], entacapone (soluble enzyme) (pK_i 9.5) [370], entacapone (membrane-bound enzyme) (pK_i 8.7) [370]
Cofactors	pyridoxal 5-phosphate	S-adenosyl methionine	–
Inhibitors	–	LY134046 (pK_i 7.6) [186]	COMT appears to exist in both membrane-bound and soluble forms. COMT has also been described to methylate steroids, particularly hydroxyestradiols
Selective inhibitors	3-hydroxybenzylhydrazine, L-α-methyldopa, benserazide [125], carbidopa	–	–
Comments	AADC is a homodimer.	–	–

Nomenclature	Monoamine oxidase A	Monoamine oxidase B
Common abbreviation	MAO-A	MAO-B
HGNC, UniProt	*MAOA*, P21397	*MAOB*, P27338
EC number	1.4.3.4 (-)-adrenaline -> 3,4-dihydroxymandelic acid + NH_3 (-)-noradrenaline -> 3,4-dihydroxymandelic acid + NH_3 tyramine -> 4-hydroxyphenyl acetaldehyde + NH_3 dopamine -> 3,4-dihydroxyphenylacetaldehyde + NH_3 5-hydroxytryptamine -> 5-hydroxyindole acetaldehyde + NH_3	1.4.3.4
Cofactors	–	flavin adenine dinucleotide +
Inhibitors	–	rasagiline (pIC_{50} 7.8) [668], phenelzine (Irreversible inhibition) (pK_i 7.8) [49], lazabemide (pK_i 7.1) [230, 599], selegiline (pK_i 5.7–6) [141, 413], tranylcypromine (pIC_{50} 4.7) [664]
Selective inhibitors	flavin adenine dinucleotide	safinamide (pK_i 6.3) [48]
Comments	moclobemide (pK_i 8.3) [284], phenelzine (Irreversible inhibition) (pK_i 7.3) [49], tranylcypromine (pIC_{50} 4.7) [664], selegiline (pK_i 4.2) [413], befloxatone [124], clorgiline, pirlindole [406]	–

Further reading on Catecholamine turnover

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Deshwal S *et al.* (2017) Emerging role of monoamine oxidase as a therapeutic target for cardiovascular disease. *Curr Opin Pharmacol* **33**: 64-69 [PMID:28528298]

Fisar Z. (2016) Drugs related to monoamine oxidase activity. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **69**: 112-24 [PMID:26944656]

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Walen K *et al.* (2017) Tyrosine and tryptophan hydroxylases as therapeutic targets in human disease. *Expert Opin. Ther. Targets* **21**: 167-180 [PMID:27973928]

Ceramide turnover

Enzymes → Ceramide turnover

Overview: Ceramides are a family of sphingophospholipids synthesized in the endoplasmic reticulum, which mediate cell stress responses, including apoptosis, autophagy and senescence, Serine palmitoyltransferase generates 3-ketosphinganine, which is reduced to sphinganine (dihydrosphingosine). N-Acylation allows the formation of dihydroceramides, which are subsequently reduced to form ceramides. Once synthesized, ceramides are trafficked from the ER to the Golgi bound to the ceramide transfer protein, CERT (*COL4A3BP*, Q9Y5P4). Ceramide can be metabolized via multiple routes, ensuring tight regulation of its cellular levels. Addition of phosphocholine generates sphingomyelin while carbohydrate is added to form glucosyl- or galactosylceramides. Ceramidase re-forms sphingosine or sphinganine from ceramide or dihydroceramide. Phosphorylation of ceramide generates ceramide phosphate. The determination of accurate kinetic parameters for many of the enzymes in the sphingolipid metabolic pathway is complicated by the lipophilic nature of the substrates.

Serine palmitoyltransferase

Enzymes → Ceramide turnover → Serine palmitoyltransferase

Overview: The functional enzyme is a heterodimer of SPT1 (LCB1) with either SPT2 (LCB2) or SPT3 (LCB2B); the small subunits of SPT (ssSPTa or ssSPTb) bind to the heterodimer to enhance enzymatic activity. The complexes of SPT1/SPT2/ssSPTa and SPT1/SPT2/ssSPTb were most active with palmitoylCoA as substrate, with the latter complex also showing some activity with stearoylCoA [234]. Complexes involving SPT3 appeared more broad in substrate selectivity, with incorporation of myristoylCoA prominent for SPT1/SPT3/ssSPTa complexes, while SP1/SPT3/ssSPTb complexes had similar activity with C16, C18 and C20 acylCoAs [234].

Nomenclature	serine palmitoyltransferase long chain base subunit 1	serine palmitoyltransferase long chain base subunit 2	serine palmitoyltransferase long chain base subunit 3	serine palmitoyltransferase small subunit A	serine palmitoyltransferase small subunit B
Common abbreviation	SPT1	SPT2	SPT3	SPTSSA	SPTSSB
HGNC, UniProt	*SPTLC1*, O15269	*SPTLC2*, O15270	*SPTLC3*, Q9NUV7	*SPTSSA*, Q969W0	*SPTSSB*, Q8NFR3
EC number	2.3.1.50: L-serine + palmitoyl-CoA -> 3-ketosphinganine + coenzyme A + CO_2	2.3.1.50: L-serine + palmitoyl-CoA -> 3-ketosphinganine + coenzyme A + CO_2	2.3.1.50: L-serine + palmitoyl-CoA -> 3-ketosphinganine + coenzyme A + CO_2	–	–
Cofactors	pyridoxal 5-phosphate	pyridoxal 5-phosphate	pyridoxal 5-phosphate	–	–
Selective inhibitors	myriocin (pK_i 9.6) [414] – Mouse	myriocin [414]	myriocin [414]	–	–

Ceramide synthase

Enzymes → Ceramide turnover → Ceramide synthase

Overview: This family of enzymes, also known as sphingosine *N*-acyltransferase, is located in the ER facing the cytosol with an as-yet undefined topology and stoichiometry. Ceramide synthase *in vitro* is sensitive to inhibition by the fungal derived toxin, fumonisin B1.

Nomenclature	ceramide synthase 1	ceramide synthase 2	ceramide synthase 3	ceramide synthase 4	ceramide synthase 5	ceramide synthase 6
Common abbreviation	CERS1	CERS2	CERS3	CERS4	CERS5	CERS6
HGNC, UniProt	*CERS1*, P27544	*CERS2*, Q96G23	*CERS3*, Q8IU89	*CERS4*, Q9HA82	*CERS5*, Q8N5B7	*CERS6*, Q6ZMG9
EC number	2.3.1.24: acylCoA + sphinganine -> dihydroceramide + coenzyme A sphingosine + acylCoA -> ceramide + coenzyme A	2.3.1.24: acylCoA + sphinganine -> dihydroceramide + coenzyme A sphingosine + acylCoA -> ceramide + coenzyme A	2.3.1.24: acylCoA + sphinganine -> dihydroceramide + coenzyme A sphingosine + acylCoA -> ceramide + coenzyme A	2.3.1.24: acylCoA + sphinganine -> dihydroceramide + coenzyme A sphingosine + acylCoA -> ceramide + coenzyme A	2.3.1.24: acylCoA + sphinganine -> dihydroceramide + coenzyme A sphingosine + acylCoA -> ceramide + coenzyme A	2.3.1.24: acylCoA + sphinganine -> dihydroceramide + coenzyme A sphingosine + acylCoA -> ceramide + coenzyme A
Substrates	C18-CoA [611]	C24- and C26-CoA [338]	C26-CoA and longer [417, 484]	C18-, C20- and C22-CoA [501]	C16-CoA [334, 501]	C14- and C16-CoA [416]

Sphingolipid Δ^4-desaturase

Enzymes → Ceramide turnover → Sphingolipid Δ^4-desaturase

Overview: DEGS1 and DEGS2 are 4TM proteins.

Nomenclature	delta 4-desaturase, sphingolipid 1	delta 4-desaturase, sphingolipid 2
HGNC, UniProt	*DEGS1*, O15121	*DEGS2*, Q6QHC5
EC number	1.14.-.-	1.14.-.-
Cofactors	NAD	NAD
Inhibitors	SKI II (pK_i 6.5) [107], RBM2-1B (pIC_{50} 4.7) [73]	–
Comments	Myristoylation of DEGS1 enhances its activity and targets it to the mitochondria [37].	–

Comments: DEGS1 activity is inhibited by a number of natural products, including curcumin and Δ^9-tetrahydrocannabinol [163].

Sphingomyelin synthase

Enzymes → Ceramide turnover → Sphingomyelin synthase

Overview: Following translocation from the ER to the Golgi under the influence of the ceramide transfer protein, sphingomyelin synthases allow the formation of sphingomyelin by the transfer of phosphocholine from the phospholipid phosphatidylcholine.
Sphingomyelin synthase-related protein 1 is structurally related but lacks sphingomyelin synthase activity.

Nomenclature	sphingomyelin synthase 1	sphingomyelin synthase 2	sterile alpha motif domain containing 8
HGNC, UniProt	*SGMS1*, Q86VZ5	*SGMS2*, Q8NHU3	*SAMD8*, Q96LT4
EC number	2.7.8.27: ceramide + phosphatidylcholine -> sphingomyelin + diacylglycerol	2.7.8.27: ceramide + phosphatidylcholine -> sphingomyelin + diacylglycerol	2.7.8.-: ceramide + phosphatidylethanolamine -> ceramide phosphoethanolamine
Inhibitors	compound 1j (pIC_{50} 5.7) [350]	compound D24 (pIC_{50} 4.9) [134]	–
Comments	–	Palmitoylation of sphingomyelin synthase 2 may allow targeting to the plasma membrane [585].	–

Sphingomyelin phosphodiesterase

Enzymes → Ceramide turnover → Sphingomyelin phosphodiesterase

Overview: Also known as sphingomyelinase.

Nomenclature	sphingomyelin phosphodiesterase 1	sphingomyelin phosphodiesterase 2	sphingomyelin phosphodiesterase 3	sphingomyelin phosphodiesterase 4	sphingomyelin phosphodiesterase acid-like 3A	sphingomyelin phosphodiesterase acid-like 3B
HGNC, UniProt	*SMPD1*, P17405	*SMPD2*, O60906	*SMPD3*, Q9NY59	*SMPD4*, Q9NXE4	*SMPDL3A*, Q92484	*SMPDL3B*, Q92485
EC number	3.1.4.12: sphingomyelin -> ceramide + phosphocholine	3.1.4.12: sphingomyelin -> ceramide + phosphocholine	3.1.4.12: sphingomyelin -> ceramide + phosphocholine	3.1.4.12: sphingomyelin -> ceramide + phosphocholine	3.1.4.-: sphingomyelin -> ceramide + phosphocholine	3.1.4.-: sphingomyelin -> ceramide + phosphocholine
Inhibitors	–	inhibitor A (pK_i 5.8) [663] – Bovine	–	–	–	–

Neutral sphingomyelinase coupling factors

Enzymes → Ceramide turnover → Neutral sphingomyelinase coupling factors

Overview: Protein FAN [4] and polycomb protein EED [469] allow coupling between TNF receptors and neutral sphingomyelinase phosphodiesterases.

Nomenclature	embryonic ectoderm development	neutral sphingomyelinase activation associated factor
HGNC, UniProt	*EED*, O75530	*NSMAF*, Q92636
Selective inhibitors	A-395 (Binding) (pK_i 9.4) [252]	–

Ceramide glucosyltransferase

Enzymes → Ceramide turnover → Ceramide glucosyltransferase

Nomenclature	UDP-glucose ceramide glucosyltransferase
HGNC, UniProt	*UGCG*, Q16739
EC number	2.4.1.80: UDP-glucose + ceramide = uridine diphosphate + glucosylceramide
Inhibitors	miglustat (pK_i 5.1) [68]
Comments	Glycoceramides are an extended family of sphingolipids, differing in the content and organization of the sugar moieties, as well as the acyl sidechains.

Acid ceramidase

Enzymes → Ceramide turnover → Acid ceramidase

Overview: The six human ceramidases may be divided on the basis of pH optimae into acid, neutral and alkaline ceramidases, which also differ in their subcellular location.

Nomenclature	N-acylsphingosine amidohydrolase 1
HGNC, UniProt	*ASAH1*, Q13510
EC number	3.5.1.23: ceramide -> sphingosine + a fatty acid
Comments	This lysosomal enzyme is proteolysed to form the mature protein made up of two chains from the same gene product [318].

Neutral ceramidases

Enzymes → Ceramide turnover → Neutral ceramidases

Overview: The six human ceramidases may be divided on the basis of pH optimae into acid, neutral and alkaline ceramidases, which also differ in their subcellular location.

Nomenclature	N-acylsphingosine amidohydrolase 2	N-acylsphingosine amidohydrolase 2B
HGNC, UniProt	*ASAH2*, Q9NR71	*ASAH2B*, P0C7U1
EC number	3.5.1.23: ceramide -> sphingosine + a fatty acid	–
Comments	The enzyme is associated with the plasma membrane [584].	–

Comments: ASAH2B appears to be an enzymatically inactive protein, which may result from gene duplication and truncation.

Alkaline ceramidases

Enzymes → Ceramide turnover → Alkaline ceramidases

Overview: The six human ceramidases may be divided on the basis of pH optimae into acid, neutral and alkaline ceramidases, which also differ in their subcellular location.

Nomenclature	alkaline ceramidase 1	alkaline ceramidase 2	alkaline ceramidase 3
HGNC, UniProt	*ACER1*, Q8TDN7	*ACER2*, Q5QJU3	*ACER3*, Q9NUN7
EC number	3.5.1.23: ceramide -> sphingosine + a fatty acid	3.5.1.23: ceramide -> sphingosine + a fatty acid	3.5.1.-
Comments	ACER1 is associated with the ER [572].	ACER2 is associated with the Golgi apparatus [657].	ACER3 is associated with the ER and Golgi apparatus [391].

Ceramide kinase

Enzymes → Ceramide turnover → Ceramide kinase

Nomenclature	ceramide kinase
HGNC, UniProt	*CERK*, Q8TCT0
EC number	2.7.1.138: ceramide + ATP -> ceramide 1-phosphate + ADP
Inhibitors	NVP 231 (pIC_{50} 7.9) [214]

Comments: A ceramide kinase-like protein has been identified in the human genome (*CERKL*, Q49MI3).

Further reading on Ceramide turnover

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Iqbal J *et al.* (2017) Sphingolipids and Lipoproteins in Health and Metabolic Disorders. *Trends Endocrinol. Metab.* **28**: 506-518 [PMID:28462811]

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Chromatin modifying enzymes

Enzymes → Chromatin modifying enzymes

Overview: Chromatin modifying enzymes, and other chromatin-modifying proteins, fall into three broad categories: **writers**, **readers** and **erasers**. The function of these proteins is to dynamically maintain cell identity and regulate processes such as differentiation, development, proliferation and genome integrity *via* recognition of specific 'marks' (covalent post-translational modifications) on histone proteins and DNA [325]. In normal cells, tissues and organs, precise co-ordination of these proteins ensures expression of only those genes required to specify phenotype or which are required at specific times, for specific functions. Chromatin modifications allow DNA modifications not coded by the DNA sequence to be passed on through the genome and underlies heritable phenomena such as X chromosome inactivation, aging, heterochromatin formation, reprogramming, and gene silencing (epigenetic control).
To date at least eight distinct types of modifications are found on histones. These include small covalent modifications such as acetylation, methylation, and phosphorylation, the attachment of larger modifiers such as ubiquitination or sumoylation, and ADP ribosylation, proline isomerization and deimination. Chromatin modifications and the functions they regulate in cells are reviewed by Kouzarides (2007) [325].
Writer proteins include the histone methyltransferases, histone acetyltransferases, some kinases and ubiquitin ligases.
Readers include proteins which contain methyl-lysine-recognition motifs such as bromodomains, chromodomains, tudor domains, PHD zinc fingers, PWWP domains and MBT domains.
Erasers include the histone demethylases and histone deacetylases (HDACs and sirtuins).
Dysregulated epigenetic control can be associated with human diseases such as cancer [161], where a wide variety of cellular and protein abberations are known to perturb chromatin structure, gene transcription and ultimately cellular pathways [35, 544]. Due to the reversible nature of epigenetic modifications, chromatin regulators are very tractable targets for drug discovery and the development of novel therapeutics. Indeed, small molecule inhibitors of writers (*e.g.* azacitidine and decitabine target the DNA methyltransferases DNMT1 and DNMT3 for the treatment of myelodysplastic syndromes [199, 637]) and erasers (*e.g.* the HDAC inhibitors vorinostat, romidepsin and belinostat for the treatment of T-cell lymphomas [177, 309]) are already being used in the clinic. The search for the next generation of compounds with improved specificity against chromatin-associated proteins is an area of intense basic and clinical research [71]. Current progress in this field is reviewed by Simó-Riudalbas and Esteller (2015) [545].

2.1.1.- Protein arginine N-methyltransferases

Enzymes → Chromatin modifying enzymes → 2.1.1.- Protein arginine N-methyltransferases

Overview: Protein arginine N-methyltransferases (PRMT, EC 2.1.1.-) encompass histone arginine *N*-methyltransferases (PRMT4, PRMT7, EC 2.1.1.125) and myelin basic protein *N*-methyltransferases (PRMT7, EC 2.1.1.126). They are dimeric or tetrameric enzymes which use S-adenosyl methionine as a methyl donor, generating S-adenosylhomocysteine as a by-product. They generate both mono-methylated and di-methylated products; these may be symmetric (SDMA) or asymmetric (N^G,N^G-dimethyl-L-arginine) versions, where both guanidine nitrogens are monomethylated or one of the two is dimethylated, respectively.

Information on members of this family may be found in the online database.

3.5.1.- Histone deacetylases (HDACs)

Overview: Histone deacetylases act as erasers of epigenetic acetylation marks on lysine residues in histones. Removal of the acetyl groups facilitates tighter packing of chromatin (heterochromatin formation) leading to transcriptional repression.
The histone deacetylase family has been classified in to five subfamilies based on phylogenetic comparison with yeast homologues:
Class I contains HDACs 1, 2, 3 and 8
Class IIa contains HDACs 4, 5, 7 and 9
Class IIb contains HDACs 6 and 10
Class III contains the sirtuins (SIRT1-7)
Class IV contains only HDAC11.
Classes I, II and IV use Zn^{+} as a co-factor, whereas catalysis by Class III enzymes requires NAD^{+} as a co-factor, and members of this subfamily have ADP-ribosylase activity in addition to protein deacetylase function [521].
HDACs have more general protein deacetylase activity, being able to deacetylate lysine residues in non-histone proteins [104] such as microtubules [270], the hsp90 chaperone [326] and the tumour suppressor p53 [377].
Dysregulated HDAC activity has been identified in cancer cells and tumour tissues [355, 509], making HDACs attractive molecular targets in the search for novel mechanisms to treat cancer [639]. Several small molecule HDAC inhibitors are already approved for clinical use: romidepsin, belinostat, vorinostat, panobinostat, belinostat, valproic acid and tucidinostat. HDACs and HDAC inhibitors currently in development as potential anti-cancer therapeutics are reviewed by Simó-Riudalbas and Esteller (2015) [545].

Nomenclature	histone deacetylase 6
HGNC, UniProt	*HDAC6*, Q9UBN7
EC number	3.5.1.98
Inhibitors	trichostatin A (pK_i 9) [61], vorinostat (pK_i 8.8) [61], romidepsin (pK_i 8) [61]
Selective inhibitors	ricolinostat (pIC_{50} 8.3) [518]

Further reading on 3.5.1.- Histone deacetylases (HDACs)

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Cyclic nucleotide turnover/signalling

Enzymes → Cyclic nucleotide turnover/signalling

Overview: Cyclic nucleotides are second messengers generated by cyclase enzymes from precursor triphosphates and hydrolysed by phosphodiesterases. The cellular actions of these cyclic nucleotides are mediated through activation of protein kinases (cAMP- and cGMP-dependent protein kinases), ion channels (cyclic nucleotide-gated, CNG, and hyperpolarization and cyclic nucleotide-gated, HCN) and guanine nucleotide exchange factors (GEFs, Epac).

Adenylyl cyclases (ACs)

Enzymes → Cyclic nucleotide turnover/signalling → Adenylyl cyclases (ACs)

Overview: Adenylyl cyclase, E.C. 4.6.1.1, converts ATP to cyclic AMP and pyrophosphate. Mammalian membrane-delimited adenylyl cyclases (**nomenclature as approved by the NC-IUPHAR Subcommittee on Adenylyl cyclases** [137]) are typically made up of two clusters of six TM domains separating two intracellular, overlapping catalytic domains that are the target for the nonselective activators $G\alpha_s$ (the stimulatory G protein α subunit) and forskolin (except AC9, [479]). Adenosine and its derivatives (*e.g.* 2′,5′-dideoxyadenosine), acting through the P-site,are inhibitors of adenylyl cyclase activity [594]. Four families of membranous adenylyl cyclase are distinguishable: calmodulin (*CALM1 CALM2 CALM3*, P62158)-stimulated (AC1, AC3 and AC8), Ca^{2+}- and Gβγ-inhibitable (AC5, AC6 and AC9), Gβγ-stimulated and Ca^{2+}-insensitive (AC2, AC4 and AC7), and forskolin-insensitive (AC9) forms. A soluble adenylyl cyclase (AC10) lacks membrane spanning regions and is insensitive to G proteins.It functions as a cytoplasmic bicarbonate (pH-insensitive) sensor [93].

Nomenclature	adenylyl cyclase 1	adenylyl cyclase 2	adenylyl cyclase 3	adenylyl cyclase 4	adenylyl cyclase 5
Common abbreviation	AC1	AC2	AC3	AC4	AC5
HGNC, UniProt	*ADCY1*, Q08828	*ADCY2*, Q08462	*ADCY3*, O60266	*ADCY4*, Q8NFM4	*ADCY5*, O95622
EC number	4.6.1.1	4.6.1.1	4.6.1.1	4.6.1.1	4.6.1.1
Endogenous activators	calmodulin (*CALM1 CALM2 CALM3*, P62158), PKC-evoked phosphorylation [283, 583]	Gβγ, PKC-evoked phosphorylation, Raf-evoked phosphorylation [91, 145, 381, 588]	calmodulin (*CALM1 CALM2 CALM3*, P62158), PKC-evoked phosphorylation [102, 283]	Gβγ [195]	PKC-evoked phophorylation, Gβγ, Raf-evoked phophorylation [145, 197, 306]
Activators	compound 45 (pIC_{50} 7.7) [506] – Bovine	FD1 [449]	–	–	FD6 [449]
Endogenous inhibitors	$G\alpha_i$, $G\alpha_o$, Gβγ [588, 589]	–	RGS2, Gβγ, CaM kinase II-evoked phosphorylation [142, 546, 633]	PKC-evoked phophorylation [680]	$G\alpha_i$, Ca^{2+}, PKA-evoked phosphorylation, Gβγ, NO [197, 258, 279, 282, 589]
Inhibitors	–	SKF-83566 [114]	–	–	NKY80 (pIC_{50} 5.2) [62, 449]
Selective inhibitors	ST034307 (pIC_{50} 5.6) [64]	–	–	–	–

Nomenclature	adenylyl cyclase 6	adenylyl cyclase 7	adenylyl cyclase 8	adenylyl cyclase 9	adenylyl cyclase 10
Common abbreviation	AC6	AC7	AC8	AC9	AC10
HGNC, UniProt	*ADCY6*, O43306	*ADCY7*, P51828	*ADCY8*, P40145	*ADCY9*, O60503	*ADCY10*, Q96PN6
EC number	4.6.1.1	4.6.1.1	4.6.1.1	4.6.1.1	–
Endogenous activators	Gβγ, Raf-evoked phosphorylation [145, 197]	Gβγ, PKC-evoked phosphorylation [39, 632]	calmodulin (*CALM1 CALM2 CALM3*, P62158) [72]	–	Bicarbonate, Ca^{2+} [93, 357]
Endogenous inhibitors	$G\alpha_i$, Ca^{2+}, PKA-evoked phosphorylation, PKC-evoked phosphorylation, NO [94, 258, 335, 589, 667]	–	PKA-evoked phosphorylation [643]	Ca^{2+}/calcineurin [461]	–
Inhibitors	NKY80 (pIC_{50} 4.8) [62]	–	–	–	KH7 (pIC_{50} 5–5.5) [256], LRE1 (pIC_{50} 5) [488]

Comments: Many of the activators and inhibitors listed are only somewhat selective or have not been tested against all AC isoforms [62, 114]. AC3 shows only modest *in vitro* activation by Ca^{2+}/CaM.

Further reading on Adenylyl cyclases (ACs)

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Wiggins SV *et al.* (2018) Pharmacological modulation of the CO_2/HCO_3^-/pH-, calcium-, and ATP-sensing soluble adenylyl cyclase. *Pharmacol Ther* **190**: 173-186 [PMID:29807057]

Wu L *et al.* (2016) Adenylate cyclase 3: a new target for anti-obesity drug development. *Obes Rev* **17**: 907-14 [PMID:27256589]

Exchange protein activated by cyclic AMP (EPACs)

Enzymes → Cyclic nucleotide turnover/signalling → Exchange protein activated by cyclic AMP (EPACs)

Overview: Epacs are members of a family of guanine nucleotide exchange factors (ENSFM00250000000899), which also includes *RapGEF5* (GFR, KIAA0277, MR-GEF, Q92565) and *RapGEFL1* (Link-GEFII, Q9UHV5). They are activated endogenously by cyclic AMP and with some pharmacological selectivity by 8-pCPT-2′-O-Me-cAMP [158]. Once activated, Epacs induce an enhanced activity of the monomeric G proteins, Rap1 and Rap2 by facilitating binding of guanosine-5′-triphosphate in place of guanosine 5′-diphosphate, leading to activation of phospholipase C [524].

Nomenclature	Rap guanine nucleotide exchange factor 3	Rap guanine nucleotide exchange factor 4
Common abbreviation	Epac1	Epac2
HGNC, UniProt	*RAPGEF3*, O95398	*RAPGEF4*, Q8WZA2
Inhibitors	ESI-09 (pIC_{50} 5.5) [15]	HJC 0350 (pIC_{50} 6.5) [89], ESI-09 (pIC_{50} 4.4–5.2) [15, 90]

Further reading on Exchange protein activated by cyclic AMP (EPACs)

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Phosphodiesterases, 3′,5′-cyclic nucleotide (PDEs)

Enzymes → Cyclic nucleotide turnover/signalling → Phosphodiesterases, 3′,5′-cyclic nucleotide (PDEs)

Overview: 3′,5′-Cyclic nucleotide phosphodiesterases (PDEs, 3′,5′-cyclic-nucleotide 5′-nucleotidohydrolase), E.C. 3.1.4.17, catalyse the hydrolysis of a 3′,5′-cyclic nucleotide (usually cyclic AMP or cyclic GMP). Isobutylmethylxanthine is a nonselective inhibitor with an IC_{50} value in the millimolar range for all isoforms except PDE 8A, 8B and 9A. A 2′,3′-cyclic nucleotide 3′-phosphodiesterase (E.C. 3.1.4.37 CNPase) activity is associated with myelin formation in the development of the CNS.

Nomenclature	phosphodiesterase 1A	phosphodiesterase 1B	phosphodiesterase 1C
Common abbreviation	PDE1A	PDE1B	PDE1C
HGNC, UniProt	*PDE1A*, P54750	*PDE1B*, Q01064	*PDE1C*, Q14123
EC number	3.1.4.17	3.1.4.17	3.1.4.17
Rank order of affinity	cyclic GMP > cyclic AMP	cyclic GMP > cyclic AMP	cyclic GMP = cyclic AMP
Endogenous activators	calmodulin (*CALM1 CALM2 CALM3*, P62158)	calmodulin (*CALM1 CALM2 CALM3*, P62158)	calmodulin (*CALM1 CALM2 CALM3*, P62158)
Endogenous inhibitors	–	–	–
Inhibitors	crisaborole (pIC_{50} 5.2) [10]	–	–
Sub/family-selective inhibitors	–	–	–
Selective inhibitors	SCH51866 (pIC_{50} 7.2) [609], vinpocetine (pIC_{50} 5.1) [372]	SCH51866 (pIC_{50} 7.2) [609]	SCH51866 (pIC_{50} 7.2) [609], vinpocetine (pIC_{50} 4.3) [372]
Comments	–	–	–

Nomenclature	phosphodiesterase 2A	phosphodiesterase 3A	phosphodiesterase 3B
Common abbreviation	PDE2A	PDE3A	PDE3B
HGNC, UniProt	*PDE2A*, O00408	*PDE3A*, Q14432	*PDE3B*, Q13370
EC number	3.1.4.17	3.1.4.17	3.1.4.17
Rank order of affinity	cyclic AMP ≫ cyclic GMP	–	–
Endogenous activators	cyclic GMP	–	–
Endogenous inhibitors	–	cyclic GMP	cyclic GMP
Inhibitors	milrinone (pIC_{50} <6.5) [571]	cilostazol (pIC_{50} 6.7) [571], inamrinone (pIC_{50} 4.8) [547]	–
Sub/family-selective inhibitors	–	–	–
Selective inhibitors	BAY607550 (pIC_{50} 8.3–8.8) [56], EHNA (pIC_{50} 5.3) [411]	cilostamide (pIC_{50} 7.5) [571], anagrelide (pIC_{50} 7.1–7.3) [295, 395, 405], milrinone (pIC_{50} 6.3–6.4) [156, 571]	cilostamide (pIC_{50} 7.3) [571], cilostazol (pIC_{50} 6.4) [571], milrinone (pIC_{50} 6) [571], inamrinone (pIC_{50} 4.5) [571]
Comments	EHNA is also an inhibitor of adenosine deaminase (E.C. 3.5.4.4).	–	–

Nomenclature	phosphodiesterase 4A	phosphodiesterase 4B	phosphodiesterase 4C	phosphodiesterase 4D	phosphodiesterase 5A
Common abbreviation	PDE4A	PDE4B	PDE4C	PDE4D	PDE5A
HGNC, UniProt	*PDE4A*, P27815	*PDE4B*, Q07343	*PDE4C*, Q08493	*PDE4D*, Q08499	*PDE5A*, O76074
EC number	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17
Rank order of affinity	cyclic AMP ≫ cyclic GMP	cyclic AMP ≫ cyclic GMP	cyclic AMP ≫ cyclic GMP	cyclic AMP ≫ cyclic GMP	cyclic GMP > cyclic AMP
Activators	–	–	–	PKA-mediated phosphorylation [265]	Protein kinase A, protein kinase G [116]
Inhibitors	ibudilast (pIC_{50} 7.3) [319], RS-25344 (pIC_{50} 7.2) [517]	roflumilast (pIC_{50} 9.4) [376], ibudilast (pIC_{50} 7.2) [319], RS-25344 (pIC_{50} 6.5) [517]	RS-25344 (pIC_{50} 8.1) [517], ibudilast (pIC_{50} 6.6) [319]	RS-25344 (pIC_{50} 8.4) [517], difamilast (pIC_{50} >7.3) [446], CBS-3595 (pIC_{50} 6.1) [13]	gisadenafil (pIC_{50} 8.9) [495], milrinone (pIC_{50} 7.3)
Sub/family-selective inhibitors	rolipram (pIC_{50} 9) [623], CDP840 (pK_i 8) [465], Ro20-1724 (pIC_{50} 6.5) [623]	rolipram (pIC_{50} 9) [623], Ro20-1724 (pIC_{50} 6.4) [623]	CDP840 (pK_i 7.7) [465], rolipram (pIC_{50} 6.5) [623], Ro20-1724 (pIC_{50} 5.4) [623]	CDP840 (pK_i 8.1) [465], rolipram (pIC_{50} 7.2) [623], Ro20-1724 (pIC_{50} 6.2) [623]	–
Selective inhibitors	YM976 (pIC_{50} 8.3) [17], apremilast (pIC_{50} 7.8) [522]	–	apremilast (pIC_{50} 6.9) [522]	apremilast (pIC_{50} 7.5) [522]	vardenafil (pIC_{50} 9.7) [60], T0156 (pIC_{50} 9.5) [418], sildenafil (pIC_{50} 8.4–9) [604, 621], tadalafil (pIC_{50} 8.5) [419], SCH51866 (pIC_{50} 7.2) [609], zaprinast (pIC_{50} 6.8) [604]

Nomenclature	phosphodiesterase 6A	phosphodiesterase 6B	phosphodiesterase 6C	phosphodiesterase 6D	phosphodiesterase 6G	phosphodiesterase 6H
Common abbreviation	PDE6A	PDE6B	PDE6C	PDE6D	PDE6G	PDE6H
HGNC, UniProt	*PDE6A*, P16499	*PDE6B*, P35913	*PDE6C*, P51160	*PDE6D*, O43924	*PDE6G*, P18545	*PDE6H*, Q13956
EC number	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17
Inhibitors	compound 53 (pIC_{50} 8) [271]	–	sildenafil (pIC_{50} 7.4) [621]	–	–	–

Nomenclature	phosphodiesterase 7A	phosphodiesterase 7B	phosphodiesterase 8A	phosphodiesterase 8B
Common abbreviation	PDE7A	PDE7B	PDE8A	PDE8B
HGNC, UniProt	*PDE7A*, Q13946	*PDE7B*, Q9NP56	*PDE8A*, O60658	*PDE8B*, O95263
EC number	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17
Rank order of affinity	cyclic AMP ≫ cyclic GMP [409]	cyclic AMP ≫ cyclic GMP [200]	cyclic AMP ≫ cyclic GMP [171]	cyclic AMP ≫ cyclic GMP [249]
Inhibitors	crisaborole (pIC_{50} 6.1) [10]	BRL50481 (pIC_{50} 4.9) [11]	–	–
Selective inhibitors	BRL50481 (pIC_{50} 6.7–6.8) [11, 553]	dipyridamole (pIC_{50} 5.7–6) [200, 520], SCH51866 (pIC_{50} 5.8) [520]	PF-04957325 (pIC_{50} 7.4) [399], dipyridamole (pIC_{50} 5.1) [171]	dipyridamole (pIC_{50} 4.3) [249]
Comments	PDE7A appears to be membrane-bound or soluble for PDE7A1 and 7A2 splice variants, respectively	–	–	–

Nomenclature	phosphodiesterase 9A	phosphodiesterase 10A	phosphodiesterase 11A
Common abbreviation	PDE9A	PDE10A	PDE11A
HGNC, UniProt	*PDE9A*, O76083	*PDE10A*, Q9Y233	*PDE11A*, Q9HCR9
EC number	3.1.4.17	3.1.4.17	3.1.4.17
Rank order of affinity	cyclic GMP ≫ cyclic AMP [170]	cyclic AMP, cyclic GMP [184]	cyclic AMP, cyclic GMP [167]
Inhibitors	SCH51866 (pIC_{50} 5.8) [170], zaprinast (pIC_{50} 4.5) [170]	–	tadalafil (pIC_{50} 6.5) [419], BC11-38 (pIC_{50} 6.5) [84]
Selective inhibitors	–	mardepodect (pIC_{50} 9.4) [613]	–

Comments: PDE1A, 1B and 1C appear to act as soluble homodimers, while PDE2A is a membrane-bound homodimer. PDE3A and PDE3B are membrane-bound.
PDE4 isoforms are essentially cyclic AMP specific. The potency of YM976 at other members of the PDE4 family has not been reported. PDE4B-D long forms are inhibited by extracellular signal-regulated kinase (ERK)-mediated phosphorylation [260, 261]. PDE4A-D splice variants can be membrane-bound or cytosolic [265]. PDE4 isoforms may be labelled with [^{3}H]rolipram.

PDE6 is a membrane-bound tetramer composed of two catalytic chains (PDE6A or PDE6C and PDE6B), an inhibitory chain (PDE6G or PDE6H) and the PDE6D chain. The enzyme is essentially cyclic GMP specific and is activated by the α-subunit of transducin ($G\alpha_t$) and inhibited by sildenafil, zaprinast and dipyridamole with potencies lower than those observed for PDE5A. Defects in PDE6B are a cause of retinitis pigmentosa and congenital stationary night blindness.

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Cytochrome P450

Enzymes → Cytochrome P450

Overview: The cytochrome P450 enzyme family (CYP450), E.C. 1.14.-.-, were originally defined by their strong absorbance at 450 nm due to the reduced carbon monoxide-complexed haem component of the cytochromes. They are an extensive family of haem-containing monooxygenases with a huge range of both endogenous and exogenous substrates. These include sterols, fat-soluble vitamins, pesticides and carcinogens as well as drugs. The substrates of some orphan CYP are not known. Listed below are the human enzymes; their relationship with rodent CYP450 enzyme activities is obscure in that the species orthologue may not catalyse the metabolism of the same substrates. Although the majority of CYP450 enzyme activities are concentrated in the liver, the extra-hepatic enzyme activities also contribute to patho/physiological processes. Genetic variation of CYP450 isoforms is widespread and likely underlies a significant proportion of the individual variation to drug administration.

CYP1 family

Enzymes → Cytochrome P450 → CYP1 family

Nomenclature	CYP1A1	CYP1A2	CYP1B1
HGNC, UniProt	*CYP1A1*, P04798	*CYP1A2*, P05177	*CYP1B1*, Q16678
EC number	1.14.1.1	1.14.1.1	1.14.1.1
Inhibitors	5H3'FPE (pIC_{50} 7.4) [359]	5H3'FPE (pIC_{50} 6.4) [359]	stilbenes [154]
Comments	CYP1A1 is an extra-hepatic enzyme. It shows a preference for linear planar aromatic molecules [561].	CYP1A2 is constitutively expressed in liver. It shows a preference for triangular planar aromatic molecules [561].	Mainly expressed in extra-hepatic tissues. Can metabolise 17β-estradiol [154], leukotrienes and eicosanoids [146]. Mutations have been associated with primary congenitial glaucoma [569]

CYP2 family

Enzymes → Cytochrome P450 → CYP2 family

Nomenclature	CYP2A6	CYP2A7	CYP2A13	CYP2B6	CYP2C8
HGNC, UniProt	*CYP2A6*, P11509	*CYP2A7*, P20853	*CYP2A13*, Q16696	*CYP2B6*, P20813	*CYP2C8*, P10632
EC number	1.14.14.1	1.14.14.1	1.14.14.1	1.14.14.1	1.14.14.1
Substrates	nicotine	–	–	–	–
Inhibitors	–	–	–	ticlopidine (pIC_{50} 6.7) [175], sibutramine (pIC_{50} 5.8) [27], thiotepa (pK_i 5.3) [620]	phenelzine (pK_i 5.1) [175]
Comments	Metabolises coumarin [660].	CYP2A7 does not incorporate haem and is functionally inactive [185]	Metabolises tobacco carcinogen, 4-methylnitrosoamino)-1-(3-pyridyl)-1-butanone [570].	Substrates include: efavirenz, bupropion, cyclophosphamide, ketamine, propofol [605].	Converts arachidonic acid to 11(R)-12(S)-epoxyeicosatrienoic acid or 14(R)-15(S)-epoxyeicosatrienoic acid [672]. Drug substrates include amodiaquine [26].

Nomenclature	CYP2C19	CYP2D6	CYP2E1	CYP2F1	CYP2J2	CYP2R1
HGNC, UniProt	*CYP2C19*, P33261	*CYP2D6*, P10635	*CYP2E1*, P05181	*CYP2F1*, P24903	*CYP2J2*, P51589	*CYP2R1*, Q6VVX0
EC number	1.14.14.51 (S)-limonene + [reduced NADPH–hemoprotein reductase] + O(2) <=> (-)-trans-carveol + [oxidized NADPH–hemoprotein reductase] + H(2)O	1.14.14.1	1.14.14.1	1.14.14.1	1.14.14.1	1.14.13.15
Inhibitors	compound 51 (pIC_{50} 7.3) [120]	–	compound 23 (pK_i 7.4) [661]	–	compound 4 (pIC_{50} 6.8) [333], terfenadine (pIC_{50} 5.1) [333]	–
Selective inhibitors	compound 30 (pK_i 7.7) [178]	–	–	–	–	–
Comments	Substrates include: omeprazole, proguanil, mephenytoin, diazepam [45, 138, 254].	Substrates include: debrisoquine, metoprolol, codeine [365].	Substrates: Ethanol, p-nitrophenol [386].	Substrate: naphthalene [345].	Converts arachidonic acid to 14(R)-15(S)-epoxyeicosatrienoic acid [652]. Hydroxylates albendazole[654]. Expressed in cardiomyocytes [556].	Converts vitamin D3 to calcifediol [96].

CYP3 family

Enzymes → Cytochrome P450 → CYP3 family

Nomenclature	CYP3A4	CYP3A5	CYP3A7	CYP3A43
HGNC, UniProt	*CYP3A4*, P08684	*CYP3A5*, P20815	*CYP3A7*, P24462	*CYP3A43*, Q9HB55
EC number	1.14.14.56: 1,8-cineole + NADPH + O_2 = 2-exo-hydroxy-1,8-cineole + $NADP^+$ + H_2O 1.14.13.97: Taurochenodeoxycholate + NADPH + O_2 = taurohyocholate + $NADP^+$ + H_2O Lithocholate + NADPH + O_2 = hyodeoxycholate + $NADP^+$ + H_2O 1.14.14.55: quinine + NADPH + O_2 = 3-hydroxyquinine + $NADP^+$ + H_2O_2	1.14.14.1	1.14.14.1	1.14.14.1
Substrates	nifedipine [225], midazolam [641]	–	–	–
Inhibitors	troleandomycin (pK_i 7.8) [534], ketoconazole (pK_i 7) [217], ritonavir (pK_i >7) [310]	ritonavir (pK_i 6.9) [175]	–	–
Comments	Metabolises a vast range of xenobiotics, including antidepressants, benzodiazepines, calcium channel blockers, and chemotherapeutic agents [675]. The active site is plastic, with both homotropic and heterotropic cooperativity observed with some substrates [534]. CYP3A4 catalyses the 25-hydroxylation of trihydroxycholestane in liver microsomes [189].	CYP3A5 is expressed extrahepatically, including in the small intestine. It has overlapping substrate specificity with CYP3A4 [126, 641].	Fetal form, rarely expressed in adults. Has overlapping substrate specificity with CYP3A4 [126, 641].	Fetal expression only and considered an orphan fCYP [224]. Testosterone may be a substrate [220].

CYP4 family

Enzymes → Cytochrome P450 → CYP4 family

Nomenclature	CYP4A11	CYP4A22	CYP4B1	CYP4F2	CYP4F3
HGNC, UniProt	*CYP4A11*, Q02928	*CYP4A22*, Q5TCH4	*CYP4B1*, P13584	*CYP4F2*, P78329	*CYP4F3*, Q08477
EC number	1.14.14.80	1.14.14.80	1.14.14.1	1.14.14.78 1.14.14.79 1.14.14.94	1.14.14.78 1.14.14.79 1.14.14.94
Inhibitors	–	–	–	17-octadecynoic acid (pK_i 5.9) [537]	–
Comments	Converts lauric acid to 12-hydroxylauric acid.	Reported to be enzymatically inactive [191].	–	Responsible for ω-hydroxylation of LTB_4, LXB_4 [415], and tocopherols, including vitamin E [559]	Responsible for ω-hydroxylation of LTB_4, LXB_4 [415], and polyunsaturated fatty acids [168, 241]

Nomenclature	CYP4F8	CYP4F11	CYP4F12	CYP4F22	CYP4V2	CYP4X1	CYP4Z1
HGNC, UniProt	*CYP4F8*, P98187	*CYP4F11*, Q9HBI6	*CYP4F12*, Q9HCS2	*CYP4F22*, Q6NT55	*CYP4V2*, Q6ZWL3	*CYP4X1*, Q8N118	*CYP4Z1*, Q86W10
EC number	1.14.14.1	1.14.14.1 1.14.14.78	1.14.14.1	1.14.14.-	1.14.14.79	1.14.14.1	1.14.14.1
Comments	Converts PGH_2 to 19-hydroxyPGH_2 [69] and 8,9-EET or 11,12-EET to 18-hydroxy-8,9-EET or 18-hydroxy-11,12-EET [435].	–	AC004597.1 (ENSG00000225607) is described as being highly similar to CYP4F12	Converts arachidonic acid to 16-HETE and 18-HETE [435].	Converts myristic acid to 14-hydroxymyristic acid [429].	Converts anandamide to 14,15-epoxyeicosatrienoic ethanolamide [566].	Converts lauric acid to 12-hydroxylauric acid.

CYP5, CYP7 and CYP8 families

Enzymes → Cytochrome P450 → CYP5, CYP7 and CYP8 families

Nomenclature	CYP5A1	CYP7A1	CYP7B1	CYP8A1	CYP8B1
Common abbreviation	Thromboxane synthase	–	–	Prostacyclin synthase	–
HGNC, UniProt	*TBXAS1*, P24557	*CYP7A1*, P22680	*CYP7B1*, O75881	*PTGIS*, Q16647	*CYP8B1*, Q9UNU6
EC number	5.3.99.5: PGH_2 = thromboxane A_2	1.14.14.23	1.14.14.29	5.3.99.4	1.14.14.139 1.14.18.8
Inhibitors	ozagrel (pIC_{50} 8.4) [259]	–	–	compound 7p (pIC_{50} >6) [166]	–
Comments	Inhibited by dazoxiben [489], camonagrel [222] and furegrelate sodium (U-63557A: PubChem CID 23663954) [213].	Converts cholesterol to 7α-hydroxycholesterol [437].	Converts dehydroepiandrosterone to 7α-DHEA [510].	Converts PGH_2 to PGI_2 [244]. Inhibited by tranylcypromine [221]	Converts 7α-hydroxycholest-4-en-3-one to 7-alpha,12α-dihydroxycholest-4-en-3-one (in rabbit) [278] in the biosynthesis of bile acids.

CYP11, CYP17, CYP19, CYP20 and CYP21 families

Enzymes → Cytochrome P450 → CYP11, CYP17, CYP19, CYP20 and CYP21 families

Nomenclature	CYP11A1	CYP11B1	CYP11B2	CYP17A1	CYP19A1	CYP20A1	CYP21A2
Common abbreviation	–	–	Aldosterone synthase	–	Aromatase	–	–
HGNC, UniProt	*CYP11A1*, P05108	*CYP11B1*, P15538	*CYP11B2*, P19099	*CYP17A1*, P05093	*CYP19A1*, P11511	*CYP20A1*, Q6UW02	*CYP21A2*, P08686
EC number	1.14.15.6	1.14.15.4	1.14.15.4 1.14.15.5	1.14.14.19 1.14.14.32	1.14.14.14	1.14.-.-	1.14.14.16
Inhibitors	mitotane [343, 353]	metyrapone (pIC_{50} 7.8) [679], mitotane	osilodrostat (pIC_{50} 9.7) [662]	abiraterone (pIC_{50} 7.1–8.4) [472, 477]	anastrozole (pIC_{50} 7.8) [424], aminoglutethimide [463]	–	(2*S*,4*S*)-ketoconazole (pIC_{50} 5.3) [512] – Rat
Selective inhibitors	–	–	–	galeterone (pIC_{50} 6.5) [238]	letrozole (pK_i 10.7) [401], exemestane (pIC_{50} 7.3) [105], testolactone (pK_i 4.5) [118]	–	–
Comments	Converts cholesterol to pregnenolone plus 4-methylpentanal.	Converts deoxycortisone and 11-deoxycortisol to cortisone and cortisol, respectively. Loss-of-function mutations are associated with familial adrenal hyperplasia and hypertension. Inhibited by metyrapone [629]	Converts corticosterone to aldosterone	Converts pregnenolone and progesterone to 17α-hydroxypregnenolone and 17α-hydroxyprogesterone, respectively. Converts 17α-hydroxypregnenolone and 17α-hydroxyprogesterone to dehydroepiandrosterone and androstenedione, respectively. Converts corticosterone to cortisol.	Converts androstenedione and testosterone to estrone and 17β-estradiol, respectively. Inhibited by anastrozole [475], and letrozole [46]	–	Converts progesterone and 17α-hydroxyprogesterone to deoxycortisone and 11-deoxycortisol, respectively

CYP24, CYP26 and CYP27 families

Enzymes → Cytochrome P450 → CYP24, CYP26 and CYP27 families

Nomenclature	CYP24A1	CYP26A1	CYP26B1	CYP26C1	CYP27A1	CYP27B1	CYP27C1
Common abbreviation	–	–	–	–	Sterol 27-hydroxylase	–	–
HGNC, UniProt	*CYP24A1*, Q07973	*CYP26A1*, O43174	*CYP26B1*, Q9NR63	*CYP26C1*, Q6V0L0	*CYP27A1*, Q02318	*CYP27B1*, O15528	*CYP27C1*, Q4G0S4
EC number	1.14.15.16	1.14.-.-	1.14.-.-	1.14.-.-	1.14.15.15	1.14.15.18	1.14.19.53
Inhibitors	MK-24 (pIC_{50} 8.1) [298], compound 3a (pIC_{50} 8.1) [298], compound 4d (pIC_{50} 4.8) [3]	–	–	–	compound 4d (pIC_{50} 7.2) [3], MK-24 (pIC_{50} <6) [298]	MK-24 (pIC_{50} 6.3) [298]	–
Selective inhibitors	–	compound 5 (pIC_{50} 9.5) [212]	–	–	–	–	–
Comments	Converts 1,25-dihydroxyvitamin D3 (calcitriol) to 1α,24R,25-trihydroxyvitamin D_3.	Converts retinoic acid to 4-hydroxyretinoic acid. Inhibited by liarozole	Converts retinoic acid to 4-hydroxyretinoic acid.	Converts retinoic acid to 4-hydroxyretinoic acid [578].	Converts cholesterol to 27-hydroxycholesterol.	Converts 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D3 (calcitriol)	Converts retinol (vitamin A1) to 3,4-didehydroretinol (vitamin A2) [328].

CYP39, CYP46 and CYP51 families

Enzymes → Cytochrome P450 → CYP39, CYP46 and CYP51 families

Nomenclature	CYP39A1	CYP46A1	CYP51A1
Common abbreviation	–	Cholesterol 24-hydroxylase	Lanosterol 14-α-demethylase
HGNC, UniProt	*CYP39A1*, Q9NYL5	*CYP46A1*, Q9Y6A2	*CYP51A1*, Q16850
EC number	1.14.14.26	1.14.14.25	–
Inhibitors	–	–	azalanstat (pK_i 9.1) [618]
Comments	Converts 24-hydroxycholesterol to 7α,24-dihydroxycholesterol [351].	Converts cholesterol to 24(S)-hydroxycholesterol.	Converts lanosterol to 4,4-dimethylcholesta-8.14.24-trienol.

Further reading on Cytochrome P450

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DNA topoisomerases

Enzymes → DNA topoisomerases

Overview: DNA topoisomerases regulate the supercoiling of nuclear DNA to influence the capacity for replication or transcription. The enzymatic function of this series of enzymes involves cutting the DNA to allow unwinding, followed by re-attachment to reseal the backbone. Members of the family are targetted in anti-cancer chemotherapy.

Nomenclature	DNA topoisomerase I	DNA topoisomerase II alpha
HGNC, UniProt	*TOP1*, P11387	*TOP2A*, P11388
EC number	5.99.1.2	5.99.1.2
Inhibitors	irinotecan [148, 586] – Bovine	etoposide (pIC_{50} 7.3), teniposide [151] – Mouse

Further reading on DNA topoisomerases

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Endocannabinoid turnover

Enzymes → Endocannabinoid turnover

Overview: The principle endocannabinoids are 2-acylglycerol esters, such as 2-arachidonoylglycerol (2-AG), and *N*-acylethanolamines, such as anandamide (*N*-arachidonoylethanolamine, AEA). The glycerol esters and ethanolamides are synthesised and hydrolysed by parallel, independent pathways. Mechanisms for release and re-uptake of endocannabinoids are unclear, although potent and selective inhibitors of facilitated diffusion of endocannabinoids across cell membranes have been developed [232]. FABP5 (Q01469) has been suggested to act as a canonical intracellular endocannabinoid transporter *in vivo* [99]. For the generation of 2-arachidonoylglycerol, the key enzyme involved is diacylglycerol lipase (DAGL), whilst several routes for anandamide synthesis have been described, the best characterized of which involves *N*-acylphosphatidylethanolamine-phospholipase D (NAPE-PLD, [543]). A transacylation enzyme which forms *N*-acylphosphatidylethanolamines has been identified as a cytosolic enzyme, *PLA2G4E* (Q3MJ16) [443]. *In vitro* experiments indicate that the endocannabinoids are also substrates for oxidative metabolism *via* cyclooxygenase, lipoxygenase and cytochrome P450 enzyme activities [14, 179, 555].

N-Acylethanolamine turnover

Enzymes → Endocannabinoid turnover → *N*-Acylethanolamine turnover

Nomenclature	*N*-Acylphosphatidylethanolamine-phospholipase D	Fatty acid amide hydrolase	Fatty acid amide hydrolase-2	*N*-Acylethanolamine acid amidase
Common abbreviation	NAPE-PLD	FAAH	FAAH2	NAAA
HGNC, UniProt	*NAPEPLD*, Q6IQ20	*FAAH*, O00519	*FAAH2*, Q6GMR7	*NAAA*, Q02083
EC number	–	3.5.1.99: anandamide + H_2O <=> arachidonic acid + ethanolamine oleamide + H_2O <=> oleic acid + NH_3	3.5.1.99: anandamide + H_2O <=> arachidonic acid + ethanolamine oleamide + H_2O <=> oleic acid + NH_3	3.5.1.-
Rank order of affinity	–	anandamide > oleamide > N-oleoylethanolamide > N-palmitoylethanolamine [634]	oleamide > N-oleoylethanolamide > anandamide > N-palmitoylethanolamine [634]	N-palmitoylethanolamine > MEA > SEA ≥ N-oleoylethanolamide > anandamide [606]
Selective inhibitors	–	ASP8477 (pIC_{50} 8.4) [628], JNJ1661010 (pIC_{50} 7.8) [308], PF750 (pIC_{50} 6.3–7.8) [7], OL135 (pIC_{50} 7.4) [634], MM-433593 (pIC_{50} 7), URB597 (pIC_{50} 6.3–7) [634], PF3845 (pIC_{50} 6.6) [8]	OL135 (pIC_{50} 7.9–8.4) [305, 634], URB597 (pIC_{50} 7.5–8.3) [305, 634], ASP8477 (pIC_{50} 7.2) [628]	F215 (pIC_{50} 8.1) [348, 349], ARN726 (Irreversible inhibition) (pIC_{50} 7.6) [499], *S*-OOPP (pIC_{50} 6.4) [557] – Rat, CCP (pIC_{50} 5.3) [601]
Comments	NAPE-PLD activity appears to be enhanced by polyamines in the physiological range [362], but fails to transphosphatidylate with alcohols [467] unlike phosphatidylcholine-specific phospholipase D.	–	The FAAH2 gene is found in many primate genomes, marsupials, and other distantly related vertebrates, but not a variety of lower placental mammals, including mouse and rat [634].	–

Comments: Routes for *N*-acylethanolamine biosynthesis other than through NAPE-PLD activity have been identified [602].

2-Acylglycerol ester turnover

Enzymes → Endocannabinoid turnover → 2-Acylglycerol ester turnover

Overview: ABHD12 is a 398-aa protein, with serine hydrolase activity. It has a molecular weight of 45 kDa. A single TM is predicted at 75-95, with an extracellular catalytic domain. ABHD12 is a monoacylglycerol hydrolase [432], but may also regulate lysophosphatidylserine levels [300]. Loss-of-function mutations in ABHD12 are associated with a disorder known as PHARC (polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataracts) [172].

Nomenclature	Diacylglycerol lipase α	Diacylglycerol lipase β	Monoacylglycerol lipase	αβ-Hydrolase 6	αβ-Hydrolase 12
Common abbreviation	DAGLα	DAGLβ	MAGL	ABHD6	–
HGNC, UniProt	*DAGLA*, Q9Y4D2	*DAGLB*, Q8NCG7	*MGLL*, Q99685	*ABHD6*, Q9BV23	*ABHD12*, Q8N2K0
EC number	3.1.1.-	3.1.1.-	3.1.1.23	3.1.1.23	3.1.1.23
Endogenous substrates	diacylglycerol	diacylglycerol	2-oleoyl glycerol = 2-arachidonoylglycerol ≫ anandamide [204]	1-arachidonoylglycerol > 2-arachidonoylglycerol > 1-oleoylglycerol > 2-oleoyl glycerol [432]	–
Inhibitors	LEI105 (pIC_{50} 8.5) [30], DH376 (pIC_{50} 8.2) [441], DO34 (pIC_{50} 8.2) [441], KT-109 (pIC_{50} 5.6) [268]	DH376 (pIC_{50} 8.6) [441], DO34 (pIC_{50} 8.1) [441], LEI105 (pIC_{50} 8.1) [30], KT-109 (pIC_{50} 7.1) [268]	MJN110 (pIC_{50} 8) [436]	–	–
Selective inhibitors	–	–	JJKK 048 (pIC_{50} 9.3) [1], KML29 (pIC_{50} 8.5) [88], JZL184 (pIC_{50} 8.1) [367]	WWL70 (pIC_{50} 7.2) [346], WWL123 (pIC_{50} 6.4) [25]	DO264 (pIC_{50} 8) [442]
Comments	–	–	–	WWL70 has also been suggested to have activity at oxidative metabolic pathways independent of ABHD6 [582].	–

Comments on Endocannabinoid turnover: Many of the compounds described as inhibitors are irreversible and so potency estimates will vary with incubation time. FAAH2 is not found in rodents [634] and a limited range of inhibitors have been assessed at this enzyme activity. 2-arachidonoylglycerol has been reported to be hydrolysed by multiple enzyme activities from neural preparations [31], including *ABHD2* (P08910) [412] and carboxylesterase 1 (*CES1*, P23141 [656]). *ABHD2* (P08910) has also been described as a triacylglycerol lipase and ester hydrolase [384], while *ABHD12* (Q8N2K0) is also able to hydrolyse lysophosphatidylserine [598]. *ABHD12* (Q8N2K0) has been described to be inhibited selectively by pentacyclic triterpenoids, such as oleanolic acid [460].

Further reading on Endocannabinoid turnover

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Eicosanoid turnover

Enzymes → Eicosanoid turnover

Overview: Eicosanoids are 20-carbon fatty acids, where the usual focus is the polyunsaturated analogue arachidonic acid and its metabolites. Arachidonic acid is thought primarily to derive from phospholipase A2 action on membrane phosphatidylcholine, and may be re-cycled to form phospholipid through conjugation with coenzyme A and subsequently glycerol derivatives. Oxidative metabolism of arachidonic acid is conducted through three major enzymatic routes: cyclooxygenases; lipoxygenases and cytochrome P450-like epoxygenases, particularly CYP2J2. Isoprostanes are structural analogues of the prostanoids (hence the nomenclature D-, E-, F-isoprostanes and isothromboxanes), which are produced in the presence of elevated free radicals in a non-enzymatic manner, leading to suggestions for their use as biomarkers of oxidative stress. Molecular targets for their action have yet to be defined.

Cyclooxygenase

Enzymes → Eicosanoid turnover → Cyclooxygenase

Overview: Prostaglandin (PG) G/H synthase, most commonly referred to as cyclooxygenase (COX, (5Z,8Z,11Z,14Z)-icosa-5,8,11,14-tetraenoate,hydrogen-donor : oxygen oxidoreductase) activity, catalyses the formation of PGG_2 from arachidonic acid. Hydroperoxidase activity inherent in the enzyme catalyses the formation of PGH_2 from PGG_2. COX-1 and -2 can be nonselectively inhibited by ibuprofen, ketoprofen, naproxen, indomethacin and paracetamol (acetaminophen). PGH_2 may then be metabolised to prostaglandins and thromboxanes by various prostaglandin synthases in an apparently tissue-dependent manner.

Nomenclature	COX-1	COX-2
HGNC, UniProt	*PTGS1*, P23219	*PTGS2*, P35354
EC number	1.14.99.1: Hydrogen donor + arachidonic acid + $2O_2$ = hydrogen acceptor + H_2O + PGH_2 arachidonic acid => PGG_2 => PGH_2 This enzyme is also associated with the following reaction:: docosahexaenoic acid => PGH_3	1.14.99.1: Hydrogen donor + arachidonic acid + $2O_2$ = hydrogen acceptor + H_2O + PGH_2 arachidonic acid => PGG_2 => PGH_2 This enzyme is also associated with the following reaction:: docosahexaenoic acid => PGH_3
Selective activators	–	SC-236 (Inhibition) (pIC_{50} 8) [464]
Inhibitors	bromfenac (pIC_{50} 8.1) [22], diclofenac (pIC_{50} 7.9) [697], meclofenamic acid (pIC_{50} 7.3) [299], flurbiprofen (pIC_{50} 7.1) [627], fenoprofen (pIC_{50} 6.8) [22], ketoprofen (pIC_{50} 6.5) [70], suprofen (pIC_{50} 6.2) [70]	benzquinamide (pIC_{50} 8.3) [22], flurbiprofen (pIC_{50} 8) [36], meclofenamic acid (pIC_{50} 7.4) [299], carprofen (pIC_{50} 7) [257], ketorolac (pIC_{50} 6.9) [615], nimesulide (pIC_{50} 6.2) [453], ketoprofen (pIC_{50} 6.2) [70]
Selective inhibitors	ketorolac (pIC_{50} 9.7) [627], FK-881 (pIC_{50} 8.3) [275], SC-560 (pIC_{50} 8.1) [551], FR122047 (pIC_{50} 7.5) [440]	celecoxib (pIC_{50} 8.7) [50], valdecoxib (pIC_{50} 8.3) [581], diclofenac (pIC_{50} 7.7) [54], rofecoxib (pIC_{50} 6.1–6.5) [627], lumiracoxib (pK_i 6.5) [55], meloxicam (pIC_{50} 6.3) [340], etoricoxib (pIC_{50} 6) [503]

Prostaglandin synthases

Enzymes → Eicosanoid turnover → Prostaglandin synthases

Overview: Subsequent to the formation of PGH_2, the cytochrome P450 activities thromboxane synthase (CYP5A1, *TBXAS1*, P24557 , EC 5.3.99.5) and prostacyclin synthase (CYP8A1, *PTGIS*, Q16647, EC 5.3.99.4) generate thromboxane A_2 and prostacyclin (PGI_2), respectively. Additionally, multiple enzyme activities are able to generate prostaglandin E_2 (PGE_2), prostaglandin D_2 (PGD_2) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). PGD_2 can be metabolised to 9α,11β-prostacyclin $F_{2\alpha}$ through the multifunctional enzyme activity of AKR1C3. PGE_2 can be metabolised to 9α,11β-prostaglandin $F_{2\alpha}$ through the 9-ketoreductase activity of CBR1. Conversion of the 15-hydroxyecosanoids, including prostaglandins, lipoxins and leukotrienes to their keto derivatives by the NAD-dependent enzyme HPGD leads to a reduction in their biological activity.

Nomenclature	CYP5A1	CYP8A1	mPGES1	mPGES2	cPGES	L-PGDS
Common abbreviation	Thromboxane synthase	Prostacyclin synthase	–	–	–	–
HGNC, UniProt	*TBXAS1*, P24557	*PTGIS*, Q16647	*PTGES*, O14684	*PTGES2*, Q9H7Z7	*PTGES3*, Q15185	*PTGDS*, P41222
EC number	5.3.99.5: PGH_2 = thromboxane A_2	5.3.99.4	5.3.99.3: PGH_2 = PGE_2	5.3.99.3: PGH_2 = PGE_2	5.3.99.3: PGH_2 = PGE_2	5.3.99.2: PGH_2 = PGD_2
Cofactors	–	–	glutathione	dihydrolipoic acid	–	–
Inhibitors	ozagrel (pIC_{50} 8.4) [259]	compound 7p (pIC_{50} >6) [166]	compound 44 (pIC_{50} 9) [207]	compound 30 (pIC_{50} <6) [502]	–	–
Selective inhibitors	–	–	compound 39 (pIC_{50} 8.4) [541]	–	–	AT-56 (pK_i 4.1) [277]
Comments	Inhibited by dazoxiben [489], camonagrel [222] and furegrelate sodium (U-63557A: PubChem CID 23663954) [213].	Converts PGH_2 to PGI_2 [244]. Inhibited by tranylcypromine [221]	–	–	Phosphorylated and activated by casein kinase 2 (CK2) [317]. Appears to regulate steroid hormone function by interaction with dimeric hsp90 [85, 292].	–

Nomenclature	H-PGDS	AKR1C3	CBR1	HPGD
HGNC, UniProt	*HPGDS*, O60760	*AKR1C3*, P42330	*CBR1*, P16152	*HPGD*, P15428
EC number	5.3.99.2: PGH_2 = PGD_2	1.3.1.20 1.1.1.188: PGD_2 + $NADP^+$ = $PGF_{2\alpha}$ + NADPH + H^+ 1.1.1.64 1.1.1.239 1.1.1.213	1.1.1.184 1.1.1.189: PGE_2 + $NADP^+$ = $PGF_{2\alpha}$ + NADPH + H^+ 1.1.1.197	1.1.1.141 15-hydroxyprostaglandins => 15-ketoprostaglandins LXA_4 => 15-keto-lipoxin A_4
Cofactors	–	$NADP^+$	$NADP^+$	–
Inhibitors	HQL-79 (pIC_{50} 5.3–5.5) [19]	tolfenamic acid (pK_i 8.1) [481] flufenamic acid, indomethacin, flavonoids such as 2′-Hydroxyflavanone (pIC_{50} 6.5) [398, 550]	wedelolactone (pIC_{50} 5.4) [681]	compound 3 (pIC_{50} 8.1) [653]
Comments	–	AKR1C3 also exhibits an hydroxysteroid dehydrogenase activity.	–	–

Comments: YS121 has been reported to inhibit mPGES1 and 5-LOX with a pIC_{50} value of 5.5 [320].

Lipoxygenases

Enzymes → Eicosanoid turnover → Lipoxygenases

Overview: The lipoxygenases (LOXs) are a structurally related family of non-heme iron dioxygenases that function in the production, and in some cases metabolism, of fatty acid hydroperoxides. For arachidonic acid as substrate, these products are hydroperoxyeicosatetraenoic acids (HPETEs). In humans there are five lipoxygenases, the 5S-(arachidonate : oxygen 5-oxidoreductase), 12R-(arachidonate 12-lipoxygenase, 12R-type), 12S-(arachidonate : oxygen 12-oxidoreductase), and two distinct 15S-(arachidonate : oxygen 15-oxidoreductase) LOXs that oxygenate arachidonic acid in different positions along the carbon chain and form the corresponding 5S-, 12S-, 12R-, or 15S-hydroperoxides, respectively.

Nomenclature	5-LOX	12R-LOX	12S-LOX	15-LOX-1	15-LOX-2	E-LOX
HGNC, UniProt	*ALOX5*, P09917	*ALOX12B*, O75342	*ALOX12*, P18054	*ALOX15*, P16050	*ALOX15B*, O15296	*ALOXE3*, Q9BYJ1
EC number	1.13.11.34: arachidonic acid + O_2 = LTA_4 + H_2O	1.13.11.31 arachidonic acid + O_2 => 12R-HPETE	1.13.11.31 arachidonic acid + O_2 => 12S-HPETE	1.13.11.33: arachidonic acid + O_2 = 15S-HPETE linoleic acid + O_2 => 13S-HPODE	1.13.11.33: arachidonic acid + O_2 = 15S-HPETE	1.13.11.-
Substrates	–	methyl arachidonate	–	–	–	–
Endogenous substrates	arachidonic acid	–	–	–	–	12R-HPETE
Endogenous activators	5-LOX activating protein (*ALOX5AP*, P20292)	–	–	–	–	–
Endogenous inhibitors	Protein kinase A-mediated phosphorylation [379]	–	–	–	–	–
Inhibitors	–	–	–	ML351 (pIC_{50} 6.7) [485]	compound 21n (pIC_{50} 7.3) [636]	–
Selective inhibitors	CJ13610 (pIC_{50} 7.2) [169], PF-04191834 (pIC_{50} 6.6) [396], zileuton (pIC_{50} 6.4) [81]	–	ML355 (pIC_{50} 6.5) [374]	compound 34 (pK_i >8) [486]	–	–
Comments	FLAP activity can be inhibited by MK-886 [147] and BAY-X1005 [245] leading to a selective inhibition of 5-LOX activity	–	–	–	Inhibited by MLS000536924 (pK_i 5.6) [286].	E-LOX metabolises the product from the 12R-lipoxygenase (12R-HPETE) to a specific epoxyalcohol compound [669].

Comments: An 8-LOX (EC 1.13.11.40, arachidonate:oxygen 8-oxidoreductase) may be the mouse orthologue of 15-LOX-2 [190]. Some general LOX inhibitors are nordihydroguiaretic acid and esculetin. Zileuton and caffeic acid are used as 5-lipoxygenase inhibitors, while baicalein and CDC are 12-lipoxygenase inhibitors. The specificity of these inhibitors has not been rigorously assessed with all LOX forms: baicalein, along with other flavonoids, such as fisetin and luteolin, also inhibits 15-LOX-1 [514].

Leukotriene and lipoxin metabolism

Enzymes → Eicosanoid turnover → Leukotriene and lipoxin metabolism

Overview: Leukotriene A_4 (LTA_4), produced by 5-LOX activity, and lipoxins may be subject to further oxidative metabolism; ω-hydroxylation is mediated by CYP4F2 and CYP4F3, while β-oxidation in mitochondria and peroxisomes proceeds in a manner dependent on coenzyme A conjugation. Conjugation of LTA_4 at the 6 position with reduced glutathione to generate LTC_4 occurs under the influence of leukotriene C_4 synthase, with the subsequent formation of LTD_4 and LTE_4, all three of which are agonists at CysLT receptors. LTD_4 formation is catalysed by γ-glutamyltransferase, and subsequently dipeptidase 2 removes the terminal glycine from LTD_4 to generate LTE_4. Leukotriene A_4 hydrolase converts the 5,6-epoxide LTA_4 to the 5-hydroxylated LTB_4, an agonist for BLT receptors. LTA_4 is also acted upon by 12S-LOX to produce the trihydroxyeicosatetraenoic acids lipoxins LXA_4 and LXB_4. Treatment with a LTA_4 hydrolase inhibitor in a murine model of allergic airway inflammation increased LXA_4 levels, in addition to reducing LTB_4, in lung lavage fluid [491]. LTA_4 hydrolase is also involved in biosynthesis of resolvin Es. Aspirin has been reported to increase endogenous formation of 18S-hydroxyeicosapentaenoate (18S-HEPE) compared with 18R-HEPE, a resolvin precursor. Both enantiomers may be metabolised by human recombinant 5-LOX; recombinant LTA_4 hydrolase converted chiral 5S(6)-epoxide-containing intermediates to resolvin E1 and 18S-resolvin E1 [444].

Nomenclature	Leukotriene C4 synthase	γ-Glutamyltransferase	Dipeptidase 1	Dipeptidase 2	Leukotriene A_4 hydrolase
HGNC, UniProt	*LTC4S*, Q16873	*GGCT*, O75223	*DPEP1*, P16444	*DPEP2*, Q9H4A9	*LTA4H*, P09960
EC number	4.4.1.20: LTC_4 = glutathione + LTA_4	2.3.2.2: (5-L-glutamyl)-peptide + an amino acid = a peptide + a 5-L-glutamyl amino acid $LTC_4 + H_2O$ => LTD_4 + L-glutamate	3.4.13.19: $LTD_4 + H_2O = LTE_4$ + glycine	3.4.13.19: $LTD_4 + H_2O = LTE_4$ + glycine	3.3.2.6
Inhibitors	example 36 (pIC_{50} 8.1) [508], compound 39 (pIC_{50} <5.5) [541]	GGsTop (pK_i 3.8) [235]	cilastatin (pK_i 6) [215]	–	bestatin (pK_i 5.4) [450]

Comments: LTA4H is a member of a family of arginyl aminopeptidases (ENSFM00250000001675), which also includes aminopeptidase B (*RNPEP*, 9H4A4) and aminopeptidase B-like 1 (*RNPEPL1*, Q9HAU8). Dipeptidase 1 and 2 are members of a family of membrane dipeptidases, which also includes (*DPEP3*, Q9H4B8) for which LTD_4 appears not to be a substrate.

Further reading on Eicosanoid turnover

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GABA turnover

Enzymes → GABA turnover

Overview: The inhibitory neurotransmitter γ-aminobutyrate (GABA, 4-aminobutyrate) is generated in neurones by glutamic acid decarboxylase. GAD1 and GAD2 are differentially expressed during development, where GAD2 is thought to subserve a trophic role in early life and is distributed throughout the cytoplasm. GAD1 is expressed in later life and is more associated with nerve terminals [160] where GABA is principally accumulated in vesicles through the action of the vesicular inhibitory amino acid transporter SLC32A1. The role of γ-aminobutyraldehyde dehydrogenase (ALDH9A1) in neurotransmitter GABA synthesis is less clear. Following release from neurons, GABA may interact with either $GABA_A$ or $GABA_B$ receptors and may be accumulated in neurones and glia through the action of members of the SLC6 family of transporters. Successive metabolism through GABA transaminase and succinate semialdehyde dehydrogenase generates succinic acid, which may be further metabolized in the mitochondria in the tricarboxylic acid cycle.

Nomenclature	Glutamic acid decarboxylase 1	Glutamic acid decarboxylase 2
Common abbreviation	GAD1	GAD2
HGNC, UniProt	*GAD1*, Q99259	*GAD2*, Q05329
EC number	4.1.1.15: L-glutamic acid + H^+ -> GABA + CO_2	4.1.1.15: L-glutamic acid + H^+ -> GABA + CO_2
Endogenous substrates	L-glutamic acid, L-aspartic acid	L-glutamic acid, L-aspartic acid
Products	GABA	GABA
Cofactors	pyridoxal 5-phosphate	pyridoxal 5-phosphate
Selective inhibitors	s-allylglycine	s-allylglycine
Comments	L-aspartic acid is a less rapidly metabolised substrate of mouse brain glutamic acid decarboxylase generating β-alanine [65]. Autoantibodies against GAD1 and GAD2 are elevated in type 1 diabetes mellitus and neurological disorders (see Further reading).	

Nomenclature	aldehyde dehydrogenase 9 family member A1	4-aminobutyrate aminotransferase	aldehyde dehydrogenase 5 family member A1
Common abbreviation	–	GABA-T	SSADH
HGNC, UniProt	*ALDH9A1*, P49189	*ABAT*, P80404	*ALDH5A1*, P51649
EC number	1.2.1.19: 4-aminobutanal + NAD + H_2O = GABA + NADH + H^+ 1.2.1.47: 4-trimethylammoniobutanal + NAD + H_2O = 4-trimethylammoniobutanoate + NADPH + $2H^+$ 1.2.1.3: an aldehyde + H_2O + NAD = a carboxylate + $2H^+$ + NADH	2.6.1.19: GABA + α-ketoglutaric acid = L-glutamic acid + 4-oxobutanoate 2.6.1.22: (S)-3-amino-2-methylpropanoate + α-ketoglutaric acid = 2-methyl-3-oxopropanoate + L-glutamic acid	1.2.1.24: 4-oxobutanoate + NAD + H_2O = succinic acid + NADH + $2H^+$ 4-hydroxy-trans-2-nonenal + NAD + H_2O = 4-hydroxy-trans-2-nonenoate + NADH + $2H^+$
Cofactors	NAD	pyridoxal 5-phosphate	NAD [536]
Inhibitors	–	vigabatrin (Irreversible inhibition) (pK_i 3.1) [356, 542]	4-acryloylphenol (pIC_{50} 6.5) [587]

Further reading on GABA turnover

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Glycerophospholipid turnover

Enzymes → Glycerophospholipid turnover

Overview: Phospholipids are the basic barrier components of membranes in eukaryotic cells divided into glycerophospholipids (phosphatidic acid, phosphatidylethanolamine, phosphatidylcholine, phosphatidylserine, phosphatidylinositol and its phosphorylated derivatives) and sphingolipids (ceramide phosphorylcholine and ceramide phosphorylethanolamine).

Phosphoinositide-specific phospholipase C

Enzymes → Glycerophospholipid turnover → Phosphoinositide-specific phospholipase C

Overview: Phosphoinositide-specific phospholipase C (PLC, EC 3.1.4.11), catalyses the hydrolysis of PIP_2 to IP_3 and 1,2-diacylglycerol, each of which have major second messenger functions. Two domains, X and Y, essential for catalytic activity, are conserved in the different forms of PLC. Isoforms of PLC-β are activated primarily by G protein-coupled receptors through members of the $G_{q/11}$ family of G proteins. The receptor-mediated activation of PLC-γ involves their phosphorylation by receptor tyrosine kinases (RTK) in response to activation of a variety of growth factor receptors and immune system receptors. PLC-ϵ1 may represent a point of convergence of signalling via both G protein-coupled and catalytic receptors. Ca^{2+} ions are required for catalytic activity of PLC isoforms and have been suggested to be the major physiological form of regulation of PLC-δ activity. PLC has been suggested to be activated non-selectively by the small molecule *m*3M3FBS [29], although this mechanism of action has been questioned [330]. The aminosteroid U73122 has been described as an inhibitor of phosphoinositide-specific PLC [552], although its selectivity among the isoforms is untested and it has been reported to occupy the H1 histamine receptor [272].

Nomenclature	PLCβ1	PLCβ2	PLCβ3	PLCβ4
HGNC, UniProt	*PLCB1*, Q9NQ66	*PLCB2*, Q00722	*PLCB3*, Q01970	*PLCB4*, Q15147
EC number	3.1.4.11: 1-phosphatidyl-1D-*myo*-inositol 4,5-bisphosphate + H_2O = 1D-*myo*-inositol 1,4,5-trisphosphate + diacylglycerol			
Endogenous activators	Gαq, Gα11, Gβγ [255, 459, 554]	Gα16, Gβγ, Rac2 (*RAC2*, P15153) [75, 273, 274, 341, 459]	Gαq, Gβγ [80, 341, 459]	Gαq [288]

Nomenclature	PLCγ1	PLCγ2	PLCδ1	PLCδ3	PLCδ4
HGNC, UniProt	*PLCG1*, P19174	*PLCG2*, P16885	*PLCD1*, P51178	*PLCD3*, Q8N3E9	*PLCD4*, Q9BRC7
EC number	3.1.4.11: 1-phosphatidyl-1D-*myo*-inositol 4,5-bisphosphate + H_2O = 1D-*myo*-inositol 1,4,5-trisphosphate + diacylglycerol				
Endogenous activators	PIP_3 [28]	PIP_3, Rac1 (*RAC1*, P63000), Rac2 (*RAC2*, P15153), Rac3 (*RAC3*, P60763) [28, 470, 619]	Transglutaminase II, p122-RhoGAP {Rat}, spermine, Gβγ [229, 262, 425, 459]	–	–
Endogenous inhibitors	–	–	Sphingomyelin [462]	–	–
Inhibitors	–	CCT129957 (pIC_{50} 5.5) [498]	–	–	–

Nomenclature	PLCε1	PLCζ1	PLCη1	PLCη2
HGNC, UniProt	*PLCE1*, Q9P212	*PLCZ1*, Q86YW0	*PLCH1*, Q4KWH8	*PLCH2*, O75038
EC number	3.1.4.11: 1-phosphatidyl-1D-*myo*-inositol 4,5-bisphosphate + H_2O = 1D-*myo*-inositol 1,4,5-trisphosphate + diacylglycerol			
Endogenous activators	Ras, rho [558, 645]	–	–	Gβγ [677]

Comments: A series of PLC-like proteins (*PLCL1*, Q15111; *PLCL2*, Q9UPR0 and *PLCH1*, Q4KWH8) form a family with PLCδ and PLCζ1 isoforms, but appear to lack catalytic activity. PLC-δ2 has been cloned from bovine sources [407].

Further reading on Phosphoinositide-specific phospholipase C

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Phospholipase A_2

Enzymes → Glycerophospholipid turnover → Phospholipase A_2

Overview: Phospholipase A_2 (PLA_2, EC 3.1.1.4) cleaves the *sn*-2 fatty acid of phospholipids, primarily phosphatidylcholine, to generate lysophosphatidylcholine and arachidonic acid. Most commonly-used inhibitors (*e.g.* bromoenol lactone, arachidonyl trifluoromethyl ketone or methyl arachidonyl fluorophosphonate) are either non-selective within the family of phospholipase A_2 enzymes or have activity against other eicosanoid-metabolising enzymes.
Secreted or extracellular forms: $sPLA_2$-1B, $sPLA_2$-2A, $sPLA_2$-2D, $sPLA_2$-2E, $sPLA_2$-2F, $sPLA_2$-3, $sPLA_2$-10 and $sPLA_2$-12A
Cytosolic, calcium-dependent forms: $cPLA_2$-4A, $cPLA_2$-4B, $cPLA_2$-4C, $cPLA_2$-4D, $cPLA_2$-4E and $cPLA_2$-4F
Other forms: PLA_2-G5, $iPLA_2$-G6, PLA_2-G7 and PAFAH2 (platelet-activating factor acetylhydrolase 2)

Nomenclature	$sPLA_2$-1B	$sPLA_2$-2A	$sPLA_2$-2D	$sPLA_2$-2E	$sPLA_2$-2F	$sPLA_2$-3
HGNC, UniProt	*PLA2G1B*, P04054	*PLA2G2A*, P14555	*PLA2G2D*, Q9UNK4	*PLA2G2E*, Q9NZK7	*PLA2G2F*, Q9BZM2	*PLA2G3*, Q9NZ20
EC number	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.4
Inhibitors	compound 28xvii (pIC_{50} 8.9) [231]	–	compound 12e (pIC_{50} 8.1) [452]	compound 12e (pIC_{50} 8.1) [452]	compound 12e (pIC_{50} 7.3) [452]	–
Comments	–	–	–	–	–	–

Nomenclature	$cPLA_2$-4A	$cPLA_2$-4B	$cPLA_2$-4C	$cPLA_2$-4D	$cPLA_2$-4E	$cPLA_2$-4F
HGNC, UniProt	*PLA2G4A*, P47712	*PLA2G4B*, P0C869	*PLA2G4C*, Q9UP65	*PLA2G4D*, Q86XP0	*PLA2G4E*, Q3MJ16	*PLA2G4F*, Q68DD2
EC number	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.4
Inhibitors	compound 57 (pIC_{50} 8.4) [375]	–	–	–	–	–
Comments	$cPLA_2$-4A also expresses lysophospholipase (EC 3.1.1.5) activity [539].	–	–	–	–	–

Nomenclature	PLA_2-G5	$iPLA_2$-G6	PLA_2-G7	$sPLA_2$-10	$sPLA_2$-12A	platelet activating factor acetylhydrolase 2
HGNC, UniProt	*PLA2G5*, P39877	*PLA2G6*, O60733	*PLA2G7*, Q13093	*PLA2G10*, O15496	*PLA2G12A*, Q9BZM1	*PAFAH2*, Q99487
EC number	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.4	3.1.1.47
Inhibitors	compound 12e (pIC_{50} 7.5) [452]	–	darapladib (pIC_{50} 10) [51]	compound 12e (pIC_{50} 7.7) [452]	–	–
Selective inhibitors	–	–	rilapladib (Competitive) (pIC_{50} 9.6) [640]	–	–	–
Comments	–	–	–	–	–	PAFAH2 also expresses PAF hydrolase activity (EC 3.1.1.47)

Comments: The sequence of PLA_2-2C suggests a lack of catalytic activity, while PLA_2-12B (GXIIB, GXIII $sPLA_2$-like) appears to be catalytically inactive [513]. A further fragment has been identified with sequence similarities to Group II PLA_2 members. Otoconin 90 (OC90) shows sequence homology to PLA_2-G10.

A binding protein for secretory phospholipase A_2 has been identified which shows modest selectivity for $sPLA_2$-1B over $sPLA_2$-2A, and also binds snake toxin phospholipase A_2 [16]. The binding protein appears to have clearance function for circulating secretory phospholipase A_2, as well as signalling functions, and is a candidate antigen for idiopathic membraneous nephropathy [38].

PLA_2-G7 and PAFAH2 also express platelet-activating factor acetylhydrolase activity (EC 3.1.1.47).

Further reading on Phospholipase A_2

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Kita Y *etal*. (2019) Cytosolic phospholipase A2 and lysophospholipid acyltransferases. *Biochim Biophys Acta Mol Cell Biol Lipids* **1864**: 838-845 [PMID:30905348]

Mouchlis VD and Dennis EA. (2019) Phospholipase A2 catalysis and lipid. mediator lipidomics. *Biochim Biophys Acta Mol Cell Biol Lipids* **1864**: 766-771 [PMID:30905345]

Murakami M *et al*. (2019) Group IID, IIE, IIF and III secreted phospholipase A2s. *Biochim Biophys Acta Mol Cell Biol Lipids*. **1864**: 803-818 [PMID:30905347]

Samuchiwal SK and Balestrieri B. (2019) Harmful and protective roles of group V phospholipase A2: Current perspectives and future directions. *Biochim Biophys Acta Mol Cell Biol Lipids* **1864**: 819-826 [PMID:30308324]

Shayman JA and Tesmer JJG. (2019) Lysosomal phospholipase A2. *Biochim Biophys Acta Mol Cell Biol Lipids*. **1864**: 932-940 [PMID:30077006]

Phosphatidylcholine-specific phospholipase D

Enzymes → Glycerophospholipid turnover → Phosphatidylcholine-specific phospholipase D

Overview: Phosphatidylcholine-specific phospholipase D (PLD, EC 3.1.4.4) catalyses the formation of phosphatidic acid from phosphatidylcholine. In addition, the enzyme can make use of alcohols, such as butanol in a transphosphatidylation reaction [490].

Nomenclature	PLD1	PLD2
HGNC, UniProt	*PLD1*, Q13393	*PLD2*, O14939
EC number	3.1.4.4	3.1.4.4 A phosphatidylcholine + H_2O <=> choline + a phosphatidate
Endogenous activators	ADP-ribosylation factor 1 (*ARF1*, P84077), PIP_2, RhoA, PKC evoked phosphorylation, RalA [233, 378]	ADP-ribosylation factor 1 (*ARF1*, P84077), PIP_2 [369], oleic acid [519]
Endogenous inhibitors	Gβγ [478]	Gβγ [478]
Inhibitors	FIPI (pIC_{50} 8) [530]	–
Selective inhibitors	compound 69 (pIC_{50} 7.3) [530]	VU0364739 (pIC_{50} 7.7) [339]

Comments: A lysophospholipase D activity (*ENPP2*, Q13822, also known as ectonucleotide pyrophosphatase/phosphodiesterase 2, phosphodiesterase I, nucleotide pyrophosphatase 2, autotaxin) has been described, which not only catalyses the production of lysophosphatidic acid (LPA) from lysophosphatidylcholine, but also cleaves ATP (see Goding *et al.*, 2003 [209]). Additionally, an N-acylethanolamine-specific phospholipase D (*NAPEPLD*, Q6IQ20) has been characterized, which appears to have a role in the generation of endocannabinoids/endovanilloids, including anandamide [448]. This enzyme activity appears to be enhanced by polyamines in the physiological range [362] and fails to transphosphatidylate with alcohols [467].

Three further, less well-characterised isoforms are PLD3 (*PLD3*, Q8IV08, other names Choline phosphatase 3, HindIII K4L homolog, Hu-K4), PLD4 (*PLD4*, Q96BZ4, other names Choline phosphatase 4, Phosphatidylcholine-hydrolyzing phospholipase, D4C14orf175 UNQ2488/PRO5775) and PLD5 (*PLD5*, Q8N7P1). PLD3 has been reported to be involved in myogenesis [451]. PLD4 is described not to have phospholipase D catalytic activity [665], but has been associated with inflammatory disorders [447, 574, 593]. Sequence analysis suggests that PLD5 is catalytically inactive.

Further reading on Phosphatidylcholine-specific phospholipase D

Brown HA *et al.* (2017) Targeting phospholipase D in cancer, infection and neurodegenerative disorders. *Nat Rev Drug Discov* **16**: 351-367 [PMID:28209987]

Frohman MA. (2015) The phospholipase D superfamily as therapeutic targets. *Trends Pharmacol. Sci.* **36**: 137-44 [PMID:25661257]

Nelson RK *et al.* (2015) Physiological and pathophysiological roles for phospholipase D. *J. Lipid Res.* **56**: 2229-37 [PMID:25926691]

Lipid phosphate phosphatases

Enzymes → Glycerophospholipid turnover → Lipid phosphate phosphatases

Overview: Lipid phosphate phosphatases, divided into phosphatidic acid phosphatases or lipins catalyse the dephosphorylation of phosphatidic acid (and other phosphorylated lipid derivatives) to generate inorganic phosphate and diacylglycerol. PTEN, a phosphatase and tensin homolog (BZS, MHAM, MMAC1, PTEN1, TEP1) is a phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase which acts as a tumour suppressor by reducing cellular levels of PI 3,4,5-P, thereby toning down activity of PDK1 and PKB. Loss-of-function mutations are frequently identified as somatic mutations in cancers.

Nomenclature	Lipin1	Lipin2	Lipin3	PPA2A	PPA2B	PPA3A	phosphatase and tensin homolog
Common abbreviation	–	–	–	–	–	–	PTEN
HGNC, UniProt	*LPIN1*, Q14693	*LPIN2*, Q92539	*LPIN3*, Q9BQK8	*PLPP1*, O14494	*PLPP3*, O14495	*PLPP2*, O43688	*PTEN*, P60484
EC number	3.1.3.4	3.1.3.4	3.1.3.4	3.1.3.4	3.1.3.4	3.1.3.4	3.1.3.67 3.1.3.48 3.1.3.16
Substrates	–	phosphatidic acid	–	–	phosphatidic acid	–	phosphatidylinositol (3,4,5)-trisphosphate

Further reading on Lipid phosphate phosphatases

Knafo S and Esteban JA. (2017) PTEN: Local and Global Modulation of Neuronal Function in Health and Disease. *Trends Neurosci* **40**: 83-91 [PMID:28081942]

Lee YR *et al.* (2018) The functions and regulation of the PTEN tumour suppressor: new modes and prospects. *Nat Rev Mol Cell Biol* **19**: 547-562 [PMID:29858604]

Yehia L *et al.* (2019) PTEN-opathies: from biological insights to evidence-based precision medicine. *J Clin Invest* **129**: 452-464 [PMID:30614812]

Phosphatidylinositol kinases

Enzymes → Glycerophospholipid turnover → Phosphatidylinositol kinases

Overview:
Phosphatidylinositol may be phosphorylated at either 3- or 4- positions on the inositol ring by PI 3-kinases or PI 4-kinases, respectively.

Phosphatidylinositol 3-kinases
Phosphatidylinositol 3-kinases (PI3K, provisional nomenclature) catalyse the introduction of a phosphate into the 3-position of phosphatidylinositol (PI), phosphatidylinositol 4-phosphate (PIP) or phosphatidylinositol 4,5-bisphosphate (PIP_2). There is evidence that PI3K can also phosphorylate serine/threonine residues on proteins. In addition to the classes described below, further serine/threonine protein kinases, including ATM (Q13315) and mTOR (P42345), have been described to phosphorylate phosphatidylinositol and have been termed PI3K-related kinases. Structurally, PI3Ks have common motifs of at least one C2, calcium-binding domain and helical domains, alongside structurally-conserved catalytic domains. Wortmannin and LY 294002 are widely-used inhibitors of PI3K activities. Wortmannin is irreversible and shows modest selectivity between Class I and Class II PI3K, while LY294002 is reversible and selective for Class I compared to Class II PI3K.

Class I PI3Ks (EC 2.7.1.153) phosphorylate phosphatidylinositol 4,5-bisphosphate to generate phosphatidylinositol 3,4,5-trisphosphate and are heterodimeric, matching catalytic and regulatory subunits. Class IA PI3Ks include p110α, p110β and p110δ catalytic subunits, with predominantly p85 and p55 regulatory subunits. The single catalytic subunit that forms Class IB PI3K is p110γ. Class IA PI3Ks are more associated with receptor tyrosine kinase pathways, while the Class IB PI3K is linked more with GPCR signalling.

Class II PI3Ks (EC 2.7.1.154) phosphorylate phosphatidylinositol to generate phosphatidylinositol 3-phosphate (and possibly phosphatidylinositol 4-phosphate to generate phosphatidylinositol 3,4-bisphosphate). Three monomeric members exist, PI3K-C2α, β and β, and include Ras-binding, Phox homology and two C2domains.

The only **class III PI3K** isoform (EC 2.7.1.137) is a heterodimer formed of a catalytic subunit (VPS34) and regulatory subunit (VPS15).

Phosphatidylinositol 4-kinases

Phosphatidylinositol 4-kinases (EC 2.7.1.67) generate phosphatidylinositol 4-phosphate and may be divided into higher molecular weight type III and lower molecular weight type II forms.

1-phosphatidylinositol 4-kinase family

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → 1-phosphatidylinositol 4-kinase family

Nomenclature	phosphatidylinositol 4-kinase alpha	phosphatidylinositol 4-kinase beta
Common abbreviation	PI4KIIIα/PIK4CA	PI4KIIIβ/PIK4CB
HGNC, UniProt	*PI4KA*, P42356	*PI4KB*, Q9UBF8
EC number	2.7.1.67	2.7.1.67
Endogenous activation	–	PKD-mediated phosphorylation [247]
Sub/family-selective inhibitors	wortmannin (pIC_{50} 6.7–6.8) [203, 408]	wortmannin (pIC_{50} 6.7–6.8) [203, 408]
Selective inhibitors	–	PIK-93 (pIC_{50} 7.7) [34, 316]

Phosphatidylinositol-4-phosphate 3-kinase family

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → Phosphatidylinositol-4-phosphate 3-kinase family

Nomenclature	phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 alpha	phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 beta	phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 gamma
Common abbreviation	C2α/PIK3C2A	C2β/PIK3C2B	C2γ/PIK3C2G
HGNC, UniProt	*PIK3C2A*, O00443	*PIK3C2B*, O00750	*PIK3C2G*, O75747
EC number	2.7.1.154	2.7.1.154	2.7.1.154
Inhibitors	torin 2 (pIC_{50} 7.6) [363]	PI-103 (pIC_{50} 8) [248]	–

Phosphatidylinositol 3-kinase family

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → Phosphatidylinositol 3-kinase family

Nomenclature	phosphatidylinositol 3-kinase catalytic subunit type 3
Common abbreviation	VPS34
HGNC, UniProt	*PIK3C3*, Q8NEB9
EC number	2.7.1.137

Phosphatidylinositol-4,5-bisphosphate 3-kinase family

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → Phosphatidylinositol-4,5-bisphosphate 3-kinase family

Overview: PI3K activation is one of the most important signal transduction pathways used to transmit signals from cell-surface receptors to regulate intracellular processes (cell growth, survival, proliferation and movement). PI3K catalytic (and regulatory) subunits play vital roles in normal cell function and in disease. Progress made in developing PI3K-targeted agents as potential therapeutics for treating cancer and other diseases is reviewed by Fruman *et al.* (2017) [182].

Nomenclature	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta
Common abbreviation	PI3Kα	PI3Kβ
HGNC, UniProt	*PIK3CA*, P42336	*PIK3CB*, P42338
EC number	2.7.1.153 2.7.11.1	2.7.1.153
Inhibitors	PIK-75 (pIC_{50} 9.5) [248], gedatolisib (pIC_{50} 9.4) [612], PF-04691502 (pK_i 9.2) [360], PI-103 (pIC_{50} 8.7) [497], BGT-226 (pIC_{50} 8.4) [392], KU-0060648 (pIC_{50} 8.4) [76], dactolisib (pIC_{50} 8.4) [388], apitolisib (pIC_{50} 8.3) [573], PIK-75 (pIC_{50} 8.2) [316]	KU-0060648 (pIC_{50} 9.3) [76], PI-103 (pIC_{50} 8.5) [497], AZD6482 (pIC_{50} 8) [438], ZSTK474 (pIC_{50} 7.4–7.8) [651, 658], apitolisib (pIC_{50} 7.6) [573], BGT-226 (pIC_{50} 7.2) [392]
Sub/family-selective inhibitors	pictilisib (pIC_{50} 8.5) [174]	pictilisib (pIC_{50} 7.5) [174]
Selective inhibitors	GSK1059615 (pIC_{50} 8.7) [315]	–

Nomenclature	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
Common abbreviation	PI3Kγ	PI3Kδ
HGNC, UniProt	*PIK3CG*, P48736	*PIK3CD*, O00329
EC number	2.7.1.153	2.7.1.153
Inhibitors	dactolisib (pIC_{50} 8.3) [388], apitolisib (pIC_{50} 7.8) [573], PI-103 (pIC_{50} 7.8) [497], BGT-226 (pIC_{50} 7.4) [392], ZSTK474 (pIC_{50} 7.3–7.3) [651, 658], TG-100-115 (pIC_{50} 7.1) [456], alpelisib (pIC_{50} 6.6) [187], KU-0060648 (pIC_{50} 6.2) [76]	KU-0060648 (pIC_{50} >10) [76], idelalisib (*in vitro* activity against recombinant enzyme) (pIC_{50} 8.6) [336], PI-103 (pIC_{50} 8.5) [497], ZSTK474 (pIC_{50} 8.2–8.3) [651, 658], apitolisib (pIC_{50} 8.2) [573], dactolisib (pIC_{50} 8.1) [388], alpelisib (pIC_{50} 6.5) [187]
Sub/family-selective inhibitors	pictilisib (pIC_{50} 7.1) [174]	pictilisib (pIC_{50} 8.5) [174]
Selective inhibitors	CZC 24832 (pIC_{50} 7.6) [42]	–

1-phosphatidylinositol-3-phosphate 5-kinase family

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → 1-phosphatidylinositol-3-phosphate 5-kinase family

Nomenclature	phosphoinositide kinase, FYVE-type zinc finger containing
HGNC, UniProt	*PIKFYVE*, Q9Y2I7
EC number	2.7.1.150: ATP + 1-phosphatidyl-1D-myo-inositol 3-phosphate = ADP + 1-phosphatidyl-1D-myo-inositol 3,5-bisphosphate

Type I PIP kinases (1-phosphatidylinositol-4-phosphate 5-kinase family)

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → Type I PIP kinases (1-phosphatidylinositol-4-phosphate 5-kinase family)

Overview: Type I PIP kinases are required for the production of the second messenger phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P2) by phosphorylating PtdIns(4)P [487]. This enzyme family is also known as type I PIP(5)Ks.

Nomenclature	phosphatidylinositol-4-phosphate 5-kinase type 1 alpha	phosphatidylinositol-4-phosphate 5-kinase type 1 gamma
Common abbreviation	PIP5K1A	PIP5K1C
HGNC, UniProt	*PIP5K1A*, Q99755	*PIP5K1C*, O60331
EC number	2.7.1.68	2.7.1.68
Inhibitors	ISA-2011B [532]	–

Type II PIP kinases (1-phosphatidylinositol-5-phosphate 4-kinase family)

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → Type II PIP kinases (1-phosphatidylinositol-5-phosphate 4-kinase family)

Overview: Type II PIP kinases are essential for the production of the second messenger phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P2) by phosphorylating PtdIns(5)P [487]. This enzyme family is also known as type II PIP(5)Ks.

Nomenclature	phosphatidylinositol-5-phosphate 4-kinase type 2 alpha	phosphatidylinositol-5-phosphate 4-kinase type 2 beta	phosphatidylinositol-5-phosphate 4-kinase type 2 gamma
Common abbreviation	PIP4K2A	PIP4K2B	PIP4K2C
HGNC, UniProt	*PIP4K2A*, P48426	*PIP4K2B*, P78356	*PIP4K2C*, Q8TBX8
EC number	2.7.1.149 ATP + 1-phosphatidyl-1D-*myo*-inositol 5-phosphate <=> ADP + 1-phosphatidyl-1D-*myo*-inositol 4,5-bisphosphate	2.7.1.149	2.7.1.149

Sphingosine kinase

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → Sphingosine kinase

Overview: SPHK1 and SPHK2 are encoded by different genes with some redundancy of function; genetic deletion of both Sphk1 and Sphk2, but not either alone, is embryonic lethal in mice. There are splice variants of each isoform (SphK1a-c and SphK2a, b), distinguished by their N-terminal sequences. SPHK1 and SPHK2 differ in tissue distribution, sub-cellular localisation, biochemical properties and regulation. They regulate discrete pools of S1P. Receptor stimulation induces SPHK1 translocation from the cytoplasm to the plasma membrane. SPHK1 translocation is regulated by phosphorylation/dephosphorylation, specific protein:protein interactions and interaction with specific lipids at the plasma membrane. SPHK1 is a dimeric protein, as confirmed by its crystal structure which forms a positive cluster, between protomers, essential for interaction with anionic phospholipids in the plasma membrane. SPHK2 is localised to the ER or associated with mitochondria or shuttles in/out of the nucleus, regulated by phosphorylation. Intracellular targets of nuclear S1P include the catalytic subunit of telomerase (TERT) and regulators of gene expression including histone deacetylases (HDAC 1/2) and peroxisome proliferator-activated receptor gamma (PPARγ). SPHK2 phosphorylates the pro-drug FTY720 (fingolimod, which is used to treat some forms of multiple sclerosis) to a mimic of S1P and that acts as a functional antagonist of $S1P_1$ receptors. Inhibitors of SPHK1 and SPHK2 have therapeutic potential in many diseases.

Nomenclature	sphingosine kinase 1	sphingosine kinase 2
Common abbreviation	SPHK1	SPHK2
HGNC, UniProt	*SPHK1*, Q9NYA1	*SPHK2*, Q9NRA0
EC number	2.7.1.91: sphingosine + ATP = sphingosine 1-phosphate + ADP dihydrosphingosine + ATP = sphingosine 1-phosphate + ADP	2.7.1.91: sphingosine + ATP = sphingosine 1-phosphate + ADP dihydrosphingosine + ATP = sphingosine 1-phosphate + ADP
Cofactors	Mg^{2+} [536]	Mg^{2+}
Inhibitors	SKI II (pK_i 4.8) [181], MP-A08 (pIC_{50} 4.6) [474]	MP-A08 (pK_i 5.2) [474], SKI II (pK_i 5.1) [196]
Selective inhibitors	PF-543 (pK_i 8.4) [527]	SLC4101431 (pK_i 7.1) [100], compound 27d (pIC_{50} 6.8) [526], opaganib (pK_i 5) [181], ROMe (pK_i 4.8) [354]
Comments	SK1 inhibitors induce its proteasomal degradation [373, 404]. SK1 crystal structures confirm that it is dimeric [5]; there is no crystal structure available for SK2.	There is no crystal structure available for SK2.

Comments: MP-A08 is competitive with ATP; other SPHK inhibitors are competitive with sphingosine. ABC294640 (opaganib) has known off-target effects on dihydroceramide desaturase (*DEGS1*) [404, 610]) and induces proteasomal degradation of SK1 [404]. ABC294640 is in clinical trials for advanced cholangiocarcinoma, advanced hepatocellular carcinoma and refractory/relapsed multiple myeloma (to view ClinicalTrials.gov list click here).

Further reading on Sphingosine kinase

Adams DR *et al.* (2016) Sphingosine Kinases: Emerging Structure-Function Insights. *Trends Biochem. Sci.* **41**: 395-409 [PMID:27021309]

Lynch KR *et al.* (2016) Sphingosine kinase inhibitors: a review of patent literature (2006-2015). *Expert Opin Ther Pat* **26**: 1409-1416 [PMID:27539678]

Pitman MR *et al.* (2016) Recent advances in the development of sphingosine kinase inhibitors. *Cell. Signal.* **28**: 1349-63 [PMID:27297359]

Pulkoski-Gross MJ *et al.* (2018) An intrinsic lipid-binding interface controls sphingosine kinase 1 function. *J. Lipid Res.* **59**: 462-474 [PMID:29326159]

Pyne NJ *et al.* (2017) Sphingosine Kinase 2 in Autoimmune/Inflammatory Disease and the Development of Sphingosine Kinase 2 Inhibitors. *Trends Pharmacol. Sci.* **38**: 581-591 [PMID:28606480]

Pyne S *et al.* (2018) Sphingosine Kinases as Druggable Targets. *Handb Exp Pharmacol* [PMID:29460151]

Nomenclature	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma	phosphatidylinositol 4-kinase type 2 beta	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta	phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 alpha	phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 beta	phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 gamma	phosphatidylinositol 3-kinase catalytic subunit type 3
Common abbreviation	PI3Kγ	PI4KIIβ/PI4K2B	PI3Kδ	C2α/PIK3C2A	C2β/PIK3C2B	C2γ/PIK3C2G	VPS34
HGNC, UniProt	*PIK3CG*, P48736	*PI4K2B*, Q8TCG2	*PIK3CD*, O00329	*PIK3C2A*, O00443	*PIK3C2B*, O00750	*PIK3C2G*, O75747	*PIK3C3*, Q8NEB9
EC number	2.7.1.153	2.7.1.67	2.7.1.153	2.7.1.154	2.7.1.154	2.7.1.154	2.7.1.137
Inhibitors	dactolisib (pIC_{50} 8.3) [388], apitolisib (pIC_{50} 7.8) [573], PI-103 (pIC_{50} 7.8) [497], BGT-226 (pIC_{50} 7.4) [392], ZSTK474 (pIC_{50} 7.3–7.3) [651, 658], TG-100-115 (pIC_{50} 7.1) [456], alpelisib (pIC_{50} 6.6) [187], KU-0060648 (pIC_{50} 6.2) [76]	–	KU-0060648 (pIC_{50} >10) [76], idelalisib (*in vitro* activity against recombinant enzyme) (pIC_{50} 8.6) [336], PI-103 (pIC_{50} 8.5) [497], ZSTK474 (pIC_{50} 8.2–8.3) [651, 658], apitolisib (pIC_{50} 8.2) [573], dactolisib (pIC_{50} 8.1) [388], alpelisib (pIC_{50} 6.5) [187]	torin 2 (pIC_{50} 7.6) [363]	PI-103 (pIC_{50} 8) [248]	–	–
Sub/family-selective inhibitors	pictilisib (pIC_{50} 7.1) [174]	adenosine (pIC_{50} 4.5–5) [577]	pictilisib (pIC_{50} 8.5) [174]	–	–	–	–
Selective inhibitors	CZC 24832 (pIC_{50} 7.6) [42]	–	–	–	–	–	–

Comments: Wortmannin also inhibits type III phosphatidylinositol 4-kinases and polo-like kinase [364]. PIK93 also inhibits PI 3-kinases [316]. Adenosine activates adenosine receptors.

Further reading on Phosphatidylinositol kinases

Raphael J *et al.* (2018) Phosphoinositide 3-kinase inhibitors in advanced breast cancer: A systematic review and meta-analysis. *Eur J Cancer* **91**: 38-46 [PMID:29331750]

Wang D *et al.* (2019) Upstream regulators of phosphoinositide 3-kinase and their role in diseases. *J Cell Physiol*. [PMID:30710358]

Goncalves MD *et al.* (2018) Phosphatidylinositol 3-Kinase, Growth Disorders, and Cancer. *N Engl J Med* **379**: 2052-2062 [PMID:30462943]

Phosphatidylinositol phosphate kinases

Enzymes → Glycerophospholipid turnover → Phosphatidylinositol phosphate kinases

Overview: PIP_2 is generated by phosphorylation of PI 4-phosphate or PI 5-phosphate by type I PI 4-phosphate 5-kinases or type II PI 5-phosphate 4-kinases.

Nomenclature	phosphatidylinositol-4-phosphate 5-kinase type 1 alpha	phosphatidylinositol-4-phosphate 5-kinase type 1 beta	phosphatidylinositol-4-phosphate 5-kinase type 1 gamma	phosphatidylinositol-5-phosphate 4-kinase type 2 alpha	phosphatidylinositol-5-phosphate 4-kinase type 2 beta	phosphatidylinositol-5-phosphate 4-kinase type 2 gamma
Common abbreviation	PIP5K1A	PIP5K1B	PIP5K1C	PIP4K2A	PIP4K2B	PIP4K2C
HGNC, UniProt	*PIP5K1A*, Q99755	*PIP5K1B*, O14986	*PIP5K1C*, O60331	*PIP4K2A*, P48426	*PIP4K2B*, P78356	*PIP4K2C*, Q8TBX8
EC number	2.7.1.68	2.7.1.68	2.7.1.68	2.7.1.149 ATP + 1-phosphatidyl-1D-*myo*-inositol 5-phosphate <=> ADP + 1-phosphatidyl-1D-*myo*-inositol 4,5-bisphosphate	2.7.1.149	2.7.1.149
Inhibitors	ISA-2011B [532]	–	–	–	–	–

Further reading on Glycerophospholipid turnover

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Irvine RF. (2016) A short history of inositol lipids. *J. Lipid Res.* **57**: 1987-1994 [PMID:27623846]

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Haem oxygenase

Enzymes → Haem oxygenase

Overview: Haem oxygenase (heme,hydrogen-donor:oxygen oxidoreductase (α-methene-oxidizing, hydroxylating)), E.C. 1.14.99.3, converts heme into biliverdin and carbon monoxide, utilizing NADPH as cofactor.

Nomenclature	Haem oxygenase 1	Haem oxygenase 2
Common abbreviation	HO1	HO2
HGNC, UniProt	*HMOX1*, P09601	*HMOX2*, P30519
EC number	1.14.14.18 Protoheme + 3 [reduced NADPH-hemoprotein reductase] + 3 O(2) <=> biliverdin + Fe(2+) + CO + 3 [oxidized NADPH-hemoprotein reductase] + 3 H(2)O	1.14.14.18 Protoheme + 3 [reduced NADPH–hemoprotein reductase] + 3 O(2) <=> biliverdin + Fe(2+) + CO + 3 [oxidized NADPH–hemoprotein reductase] + 3 H(2)O
Inhibitors	–	compound 1 (pIC_{50} 3.5) [616] – Rat

Comments: The existence of a third non-catalytic version of haem oxygenase, HO3, has been proposed, although this has been suggested to be a pseudogene [250]. The chemical tin protoporphyrin IX acts as a haem oxygenase inhibitor in rat liver with an IC_{50} value of 11 nM [152].

Further reading on Haem oxygenase

Magierowska K *et al.* (2018) Emerging role of carbon monoxide in regulation of cellular pathways and in the maintenance of gastric mucosal integrity. *Pharmacol Res* **129**: 56-64 [PMID:29360501]

Rochette L *et al.* (2018) Redox Functions of Heme Oxygenase-1 and Biliverdin Reductase in Diabetes Trends. *Endocrinol Metab.* **29**: 74-85 [PMID:29249571]

Salerno L *et al.* (2017) Heme oxygenase-1: A new druggable target in the management of chronic and acute myeloid leukemia. *Eur J Med Chem.* **142**: 163-178 [PMID:28756878]

Sebastian VP *et al.* (2018) Heme Oxygenase-1 as a Modulator of Intestinal Inflammation Development and Progression. *Front Immunol.* **9**: 1956 [PMID:30258436]

Tomczyk M *et al.* (2019) Modulation of the monocyte/macrophage system in heart failure by targeting heme oxygenase-1. *Vascul Pharmacol.* **112**: 79-90 [PMID:30213580]

Vijayan V *et al.* (2018) The macrophage heme-heme oxygenase-1 system and its role in inflammation. *Biochem Pharmacol.* **153**: 159-167 [PMID:29452096]

Hydrogen sulphide synthesis

Enzymes → Hydrogen sulphide synthesis

Overview: Hydrogen sulfide is a gasotransmitter, with similarities to nitric oxide and carbon monoxide. Although the enzymes indicated below have multiple enzymatic activities, the focus here is the generation of hydrogen sulphide (H_2S) and the enzymatic characteristics are described accordingly. Cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) are pyridoxal phosphate (PLP)-dependent enzymes. 3-mercaptopyruvate sulfurtransferase (3-MPST) functions to generate H_2S; only CAT is PLP-dependent, while 3-MPST is not. Thus, this third pathway is sometimes referred to as PLP-independent. CBS and CSE are predominantly cytosolic enzymes, while 3-MPST is found both in the cytosol and the mitochondria. For an authoritative review on the pharmacological modulation of H_2S levels, see Szabo and Papapetropoulos, 2017 [575].

Nomenclature	Cystathionine β-synthase	Cystathionine γ-lyase	L-Cysteine:2-oxoglutarate aminotransferase	3-Mercaptopyruvate sulfurtransferase
Common abbreviation	CBS	CSE	CAT	MPST
HGNC, UniProt	*CBS*, P35520	*CTH*, P32929	*KYAT1*, Q16773	*MPST*, P25325
EC number	4.2.1.22	4.4.1.1	4.4.1.13	2.8.1.2
Endogenous substrates	L-cysteine (K_m 6×10^{-3}M) [92], L-homocysteine [92]	L-cysteine	L-cysteine	3-mercaptopyruvic acid (K_m 1.2×10^{-3}M) [426]
Products	cystathionine	NH_3, pyruvic acid	NH_3, pyruvic acid	pyruvic acid
Cofactors	pyridoxal 5-phosphate	pyridoxal 5-phosphate	pyridoxal 5-phosphate	Zn^{2+}
Inhibitors	aminooxyacetic acid (pIC_{50} 5.1) [20]	aminoethoxyvinylglycine (pIC_{50} 6) [20], aminooxyacetic acid (pIC_{50} 6) [20], β-Cyano-L-alanine (pIC_{50} 5.8) [20], propargylglycine (pIC_{50} 4.4) [20]	–	I3MT-3 (pIC_{50} 5.6) [237]

Further reading on Hydrogen sulphide synthesis

Asimakopoulou A *et al.* (2013) Selectivity of commonly used pharmacological inhibitors for cystathionine β synthase (CBS) and cystathionine γ lyase (CSE). *Br J Pharmacol.* **169**: 922-32 [PMID:23488457]

Szabo C *et al.* (2017) International Union of Basic and Clinical Pharmacology. CII: Pharmacological Modulation of H2S Levels: H2S Donors and H2S Biosynthesis Inhibitors. *Pharmacol. Rev.* **69**: 497-564 [PMID:28978633]

Hydrolases

Enzymes → Hydrolases

Overview: Listed in this section are hydrolases not accumulated in other parts of the Concise Guide, such as monoacylglycerol lipase and acetylcholinesterase. Pancreatic lipase is the predominant mechanism of fat digestion in the alimentary system; its inhibition is associated with decreased fat absorption. CES1 is present at lower levels in the gut than CES2 (P23141), but predominates in the liver, where it is responsible for the hydrolysis of many aliphatic, aromatic and steroid esters. Hormone-sensitive lipase is also a relatively non-selective esterase associated with steroid ester hydrolysis and triglyceride metabolism, particularly in adipose tissue. Endothelial lipase is secreted from endothelial cells and regulates circulating cholesterol in high density lipoproteins.

Nomenclature	pancreatic lipase	lipase E, hormone sensitive type	lipase G, endothelial type	carboxylesterase 1	ectonucleoside triphosphate diphosphohydrolase 1	ectonucleoside triphosphate diphosphohydrolase 2
Systematic nomenclature	–	–	–	–	CD39	CD39L1
Common abbreviation	PNLIP	LIPE	LIPG	CES1	NTPDase-1	NTPDase-2
HGNC, UniProt	*PNLIP*, P16233	*LIPE*, Q05469	*LIPG*, Q9Y5X9	*CES1*, P23141	*ENTPD1*, P49961	*ENTPD2*, Q9Y5L3
EC number	3.1.1.3	3.1.1.79	3.1.1.3	3.1.1.1	3.6.1.5 Hydrolyzes NTPs to nucleotide monophosphates (NMPs): A nucleoside 5′-triphosphate + 2 H_2O <=> a nucleoside 5′-phosphate + 2 phosphate	3.6.1.- Hydrolyzes extracellular nucleotide 5′-triphosphates: NTP>NMP + 2 phosphate
Inhibitors	orlistat (pIC_{50} 8.9) [66]	–	–	–	–	–
Selective inhibitors	–	–	–	–	–	PSB-6426 (pK_i 5.1) [63]
Comments	–	–	–	–	ENTPD1 sequentially converts extracellular purine nucleotides (ATP and ADP) to the monophosphate form. Adenosine is then generated by the action of Ecto-5′-Nucleotidase (CD73). ENTPD1 is the rate-limiting step. Extracellular ATP acts as a damage-associated molecular pattern (DAMP) that activates innate immune cells through adenosine-induced activation of P2X and P2Y purinogenic receptors.	–

Further reading on Hydrolases

Allard B *et al.*. (2017) The ectonucleotidases CD39 and CD73: Novel checkpoint inhibitor targets. *Immunol Rev.* **276**: 121-144 [PMID:28258700]

Kishore BK *et al.* (2018) CD39-adenosinergic axis in renal pathophysiology and therapeutics. *Purinergic Signal* **14**: 109-120 [PMID:29332180]

Rasmussen HB *et al.* (2018) Carboxylesterase 1 genes: systematic review and evaluation of existing genotyping procedures. *Drug Metab Pers Ther* **33**: 3-14 [PMID:29427553]

Zou LW *et al.* (2018) Carboxylesterase Inhibitors: An Update. *Curr Med Chem.* **25**: 1627-1649 [PMID:29210644]

Inositol phosphate turnover

Enzymes → Inositol phosphate turnover

Overview: The sugar alcohol D-*myo*-inositol is a component of the phosphatidylinositol signalling cycle, where the principal second messenger is inositol 1,4,5-trisphosphate, IP_3, which acts at intracellular ligand-gated ion channels, IP_3 receptors to elevate intracellular calcium. IP_3 is recycled to inositol by phosphatases or phosphorylated to form other active inositol polyphosphates. Inositol produced from dephosphorylation of IP_3 is recycled into membrane phospholipid under the influence of phosphatidyinositol synthase activity (CDP-diacylglycerol-inositol 3-phosphatidyltransferase [EC 2.7.8.11]).

Inositol 1,4,5-trisphosphate 3-kinases

Enzymes → Inositol phosphate turnover → Inositol 1,4,5-trisphosphate 3-kinases

Overview: Inositol 1,4,5-trisphosphate 3-kinases (E.C. 2.7.1.127, ENSFM00250000001260) catalyse the generation of inositol 1,3,4,5-tetrakisphosphate (IP_4) from IP_3. IP_3 kinase activity is enhanced in the presence of calcium/calmodulin (*CALM1 CALM2 CALM3*, P62158) [113].

Information on members of this family may be found in the online database.

Inositol polyphosphate phosphatases

Enzymes → Inositol phosphate turnover → Inositol polyphosphate phosphatases

Overview: Members of this family exhibit phosphatase activity towards IP_3, as well as towards other inositol derivatives, including the phospholipids PIP_2 and PIP_3. With IP_3 as substrate, 1-phosphatase (EC 3.1.3.57) generates 4,5,-IP_2, 4-phosphatases (EC 3.1.3.66, ENSFM00250000001432) generate 1,5,-IP_2 and 5-phosphatases (E.C. 3.1.3.36 or 3.1.3.56) generate 1,4,-IP_2.

Information on members of this family may be found in the online database.

Comments: *In vitro* analysis suggested IP_3 and IP_4 were poor substrates for SKIP, synaptojanin 1 and synaptojanin 2, but suggested that PIP_2 and PIP_3 were more efficiently hydrolysed [523].

Inositol monophosphatase

Enzymes → Inositol phosphate turnover → Inositol monophosphatase

Overview: Inositol monophosphatase (E.C. 3.1.3.25, IMPase, *myo*-inositol-1(or 4)-phosphate phosphohydrolase) is a magnesium-dependent homodimer which hydrolyses *myo*-inositol monophosphate to generate *myo*-inositol and phosphate. Glycerol may be a physiological phosphate acceptor. Li^+ is a nonselective un-competitive inhibitor more potent at IMPase 1 (pK_i *ca.* 3.5, [402]; pIC_{50} 3.2, [445]) than IMPase 2 (pIC_{50} 1.8-2.1, [445]). IMPase activity may be inhibited competitively by L690330 (pK_i 5.5, [402]), although the enzyme selectivity is not yet established.

Nomenclature	IMPase 1	IMPase 2
HGNC, UniProt	*IMPA1*, P29218	*IMPA2*, O14732
EC number	3.1.3.25	3.1.3.25
Rank order of affinity	inositol 4-phosphate > inositol 3-phosphate > inositol 1-phosphate [402]	–
Inhibitors	Li^+ (pK_i 3.5) [402]	–

Comments: Polymorphisms in either of the genes encoding these enzymes have been linked with bipolar disorder [548, 549, 666]. Disruption of the gene encoding IMPase 1, but not IMPase 2, appears to mimic the effects of Li^+ in mice [121, 122].

Further reading on Inositol phosphate turnover

Irvine R. (2016) A tale of two inositol trisphosphates. *Biochem. Soc. Trans.* **44**: 202-11 [PMID:26862207]

Livermore TM *et al.* (2016) Phosphate, inositol and polyphosphates. *Biochem. Soc. Trans.* **44**: 253-9 [PMID:26862212]

Miyamoto A *et al.* (2017) Probes for manipulating and monitoring IP_3. *Cell Calcium* **64**: 57-64 [PMID:27887748]

Windhorst S *et al.* (2017) Inositol-1,4,5-trisphosphate 3-kinase-A (ITPKA) is frequently over-expressed and functions as an oncogene in several tumor types. *Biochem. Pharmacol.* **137**: 1-9 [PMID:28377279]

Kinases (EC 2.7.x.x)

Enzymes → Kinases (EC 2.7.x.x)

Overview: Protein kinases (E.C. 2.7.11.-) use the co-substrate ATP to phosphorylate serine and/or threonine residues on target proteins. Analysis of the human genome suggests the presence of 518 protein kinases in man (divided into 15 subfamilies), with over 100 protein kinase-like pseudogenes [390]. It is beyond the scope of the Concise Guide to list all these protein kinase activities, but full listings are available on the 'Detailed page' provided for each enzyme.

Most inhibitors of these enzymes have been assessed in cell-free investigations and so may appear to 'lose' potency and selectivity in intact cell assays. In particular, ambient ATP concentrations may be influential in responses to inhibitors, since the majority are directed at the ATP binding site [128] .

Rho kinase

Enzymes → Kinases (EC 2.7.x.x) → AGC: Containing PKA, PKG, PKC families → DMPK family → Rho kinase

Overview: Rho kinase (also known as P160ROCK, Rho-activated kinase) is activated by members of the Rho small G protein family, which are activated by GTP exchange factors, such as *ARHGEF1* (Q92888, p115-RhoGEF), which in turn may be activated by $G\alpha_{12/13}$ subunits [327].

Nomenclature	Rho associated coiled-coil containing protein kinase 1	Rho associated coiled-coil containing protein kinase 2
Systematic nomenclature	ROCK1	ROCK2
Common abbreviation	Rho kinase 1	Rho kinase 2
HGNC, UniProt	*ROCK1*, Q13464	*ROCK2*, O75116
EC number	2.7.11.1	2.7.11.1
Inhibitors	RKI-1447 (pIC_{50} >9) [473], Y27632 (pIC_{50} 5.9–7.3) [383, 648], fasudil (pK_i 7) [496], Y27632 (pK_i 6.8) [607], fasudil (pIC_{50} 5.5–5.6) [383, 496]	RKI-1447 (pIC_{50} >9) [473], compound 11d [DOI: 10.1039/c0md00194e] (pIC_{50} >9) [95], GSK269962A (pIC_{50} 8.4) [149], compound 32 (pIC_{50} 8.4) [58], compound 22 (pIC_{50} 7.7) [648], Y27632 (pIC_{50} 6.3–7.2) [383, 648], Y27632 (pK_i 6.8–6.9) [383, 607], fasudil (pIC_{50} 5.9–5.9) [383, 496]
Selective inhibitors	GSK269962A (pIC_{50} 8.8) [149]	–

Further reading on Rho kinase

Feng Y *et al.* (2016) Rho Kinase (ROCK) Inhibitors and Their Therapeutic Potential. *J. Med. Chem.* **59**: 2269-300 [PMID:26486225]

Nishioka T *et al.* (2015) Developing novel methods to search for substrates of protein kinases such as Rho-kinase. *Biochim. Biophys. Acta* **1854**: 1663-6 [PMID:25770685]

Shimokawa H *et al.* (2016) RhoA/Rho-Kinase in the Cardiovascular System. *Circ. Res.* **118**: 352-66 [PMID:26838319]

Protein kinase C (PKC) family

Enzymes → Kinases (EC 2.7.x.x) → AGC: Containing PKA, PKG, PKC families → Protein kinase C (PKC) family

Overview: Protein kinase C is the target for the tumour-promoting phorbol esters, such as tetradecanoyl-β-phorbol acetate (TPA, also known as phorbol 12-myristate 13-acetate).

Classical protein kinase C isoforms: **PKCα, PKCβ, and PKCγ** are activated by Ca^{2+} and diacylglycerol, and may be inhibited by GF109203X, calphostin C, Gö 6983, chelerythrine and Ro31-8220.

Novel protein kinase C isoforms: **PKCδ, PKCε, PKCη, PKCϑ and PKCμ** are activated by diacylglycerol and may be inhibited by calphostin C, Gö 6983 and chelerythrine.

Atypical protein kinase C isoforms: **PKCι, PKCζ**.

Alpha subfamily

Enzymes → Kinases (EC 2.7.x.x) → AGC: Containing PKA, PKG, PKC families → Protein kinase C (PKC) family → Alpha subfamily

Nomenclature	protein kinase C beta	protein kinase C gamma
Common abbreviation	PKCβ	PKCγ
HGNC, UniProt	*PRKCB*, P05771	*PRKCG*, P05129
EC number	2.7.11.13	2.7.11.13
Inhibitors	sotrastaurin (pIC_{50} 8.7) [617], Gö 6983 (pIC_{50} 8.1) [223], GF109203X (pIC_{50} 7.8) [600] – Bovine, 7-hydroxystaurosporine (pIC_{50} 7.5) [535]	Gö 6983 (pIC_{50} 8.2) [223], 7-hydroxystaurosporine (pIC_{50} 7.5) [535]
Selective inhibitors	ruboxistaurin (pIC_{50} 8.2) [289], enzastaurin (pIC_{50} 7.5) [165], CGP53353 (pIC_{50} 6.4) [86]	–

Delta subfamily

Enzymes → Kinases (EC 2.7.x.x) → AGC: Containing PKA, PKG, PKC families → Protein kinase C (PKC) family → Delta subfamily

Nomenclature	protein kinase C alpha	protein kinase C delta
Common abbreviation	PKCα	PKCδ
HGNC, UniProt	*PRKCA*, P17252	*PRKCD*, Q05655
EC number	2.7.11.13	2.7.11.13
Activators	–	ingenol mebutate (pK_i 9.4) [307]
Inhibitors	sotrastaurin (pIC_{50} 8.7) [617], Gö 6983 (pIC_{50} 8.1) [223], 7-hydroxystaurosporine (pIC_{50} 7.5) [535]	sotrastaurin (pIC_{50} 8.9) [617], Gö 6983 (pIC_{50} 8) [223]

Eta subfamily

Enzymes → Kinases (EC 2.7.x.x) → AGC: Containing PKA, PKG, PKC families → Protein kinase C (PKC) family → Eta subfamily

Nomenclature	protein kinase C epsilon
Common abbreviation	PKCϵ
HGNC, UniProt	*PRKCE*, Q02156
EC number	2.7.11.13
Inhibitors	sotrastaurin (pIC_{50} 8.2) [617]

Further reading on Protein kinase C (PKC) family

Igumenova TI. (2015) Dynamics and Membrane Interactions of Protein Kinase C. *Biochemistry* **54**: 4953-68 [PMID:26214365]

Newton AC *et al.* (2017) Reversing the Paradigm: Protein Kinase C as a Tumor Suppressor. *Trends Pharmacol. Sci.* **38**: 438-447 [PMID:28283201]

Salzer E *et al.* (2016) Protein Kinase C δ: a Gatekeeper of Immune Homeostasis. *J. Clin. Immunol.* **36**: 631-40 [PMID:27541826]

FRAP subfamily

Enzymes → Kinases (EC 2.7.x.x) → Atypical → Phosphatidyl inositol 3' kinase-related kinases (PIKK) family → FRAP subfamily

Nomenclature	mechanistic target of rapamycin kinase
Common abbreviation	mTOR
HGNC, UniProt	*MTOR*, P42345
EC number	2.7.11.1
Inhibitors	ridaforolimus (pIC_{50} 9.7) [505], torin 1 (pIC_{50} 9.5) [361], sapanisertib (pIC_{50} 9) [267], sapanisertib (pK_i 8.9) [267], gedatolisib (pIC_{50} 8.8) [612], dactolisib (pIC_{50} 8.2) [388], PP121 (pIC_{50} 8) [18], XL388 (pIC_{50} 8) [580], PF-04691502 (pK_i 7.8) [360], apitolisib (pK_i 7.8) [573]
Selective inhibitors	everolimus (pIC_{50} 8.7) [531], PP-242 (pIC_{50} 8.1) [18], temsirolimus (pIC_{50} 5.8) [323]

Further reading on FRAP subfamily

Hukelmann JL *et al.* (2016) The cytotoxic T cell proteome and its shaping by the kinase mTOR. *Nat. Immunol.* **17**: 104-12 [PMID:26551880]

Saxton RA *et al.* (2017) mTOR Signaling in Growth, Metabolism, and Disease. *Cell* **169**: 361-371 [PMID:28388417]

Cyclin-dependent kinase (CDK) family

Enzymes → Kinases (EC 2.7.x.x) → CMGC: Containing CDK, MAPK, GSK3, CLK families → Cyclin-dependent kinase (CDK) family

Overview: Five of the cyclin-dependent kinases (CDKs: 7, 8, 9, 12, and 13) are involved in the phosphorylation of serine residues in the C-terminal domain of RNA polymerase II, the enzyme that is responsible for the transcription of protein-coding genes into mRNA in eukaryotes. Phosphorylation of RNA polymerase II at Ser5 is essential for transcriptional initiation, and phosphorylation of Ser 2 contributes to transcriptional elongation and termination. All five of the C-terminal domain kinases can phosphorylate Ser5, but only CDK9, CDK12, and CDK13 can phosphorylate at Ser2 [59, 321, 352].

CDK4 subfamily

Enzymes → Kinases (EC 2.7.x.x) → CMGC: Containing CDK, MAPK, GSK3, CLK families → Cyclin-dependent kinase (CDK) family → CDK4 subfamily

Nomenclature	cyclin dependent kinase 4	cyclin dependent kinase 6
Common abbreviation	CDK4	CDK6
HGNC, UniProt	*CDK4*, P11802	*CDK6*, Q00534
EC number	2.7.11.22	2.7.11.22
Inhibitors	R547 (pK_i 9) [135], palbociclib (pIC_{50} 8) [183], Ro-0505124 (pIC_{50} 7.7) [144], riviciclib (pIC_{50} 7.2) [297], alvocidib (pK_i 7.2) [79]	palbociclib (pIC_{50} 7.8) [183]

Comments on Cyclin-dependent kinase (CDK) family: The development of CDK inhibitors as anticancer drugs is reviewed in [576], with detailed content covering CDK4 and CDK6 inhibitors that are under clinical evaluation. Data produced by Jorda et al. (2018) highlights the caution that must be used when deploying commercially available CDK inhibitors as pharmacological probes [296], as most of them are more promiscuous in their selectivity than indicated. To make their findings easily accessible the Jorda data is hosted on the cyclin-dependent kinase inhibitor database (CDKiDB).

GSK subfamily

Enzymes → Kinases (EC 2.7.x.x) → CMGC: Containing CDK, MAPK, GSK3, CLK families → Glycogen synthase kinase (GSK) family → GSK subfamily

Nomenclature	glycogen synthase kinase 3 beta
Common abbreviation	GSK3B
HGNC, UniProt	*GSK3B*, P49841
EC number	2.7.11.26
Inhibitors	CHIR-98014 (pIC_{50} 9.2) [504], LY2090314 (pIC_{50} 9) [157], CHIR-99021 (pIC_{50} 8.2) [504], SB 216763 (pIC_{50} ~8.1) [109], 1-azakenpaullone (pIC_{50} 7.7) [331], SB-415286 (pIC_{50} ~7.4) [109], IM-12 (pIC_{50} 7.3) [525]
Selective inhibitors	AZD2858 (pK_i 8.3) [41]
Comments	Due to its Tau phosphorylating activity, small molecule inhibitors of GSK-3β are being investigated as potential treatments for Alzheimer's disease (AD) [41]. GSK-3β also plays a role in canonical Wnt pathway signalling, the normal activity of which is crucial for the maintenance of normal bone mass. It is hypothesised that small molecule inhibitors of GSK-3β may provide effective therapeutics for the treatment of diseases characterised by low bone mass [393].

Further reading on GSK subfamily

Beurel E *et al.* (2015) Glycogen synthase kinase-3 (GSK3): regulation, actions, and diseases. *Pharmacol. Ther.* **148**: 114-31 [PMID:25435019]

Domoto T *et al.* (2016) Glycogen synthase kinase-3β is a pivotal mediator of cancer invasion and resistance to therapy. *Cancer Sci.* **107**: 1363-1372 [PMID:27486911]

Khan I *et al.* (2017) Natural and synthetic bioactive inhibitors of glycogen synthase kinase. *Eur J Med Chem* **125**: 464-477 [PMID:27689729]

Maqbool M *et al.* (2016) Pivotal role of glycogen synthase kinase-3: A therapeutic target for Alzheimer's disease. *Eur J Med Chem* **107**: 63-81 [PMID:26562543]

Polo-like kinase (PLK) family

Enzymes → Kinases (EC 2.7.x.x) → Other protein kinases → Polo-like kinase (PLK) family

Nomenclature	polo like kinase 4
Common abbreviation	PLK4
HGNC, UniProt	*PLK4*, O00444
EC number	2.7.11.21
Inhibitors	CFI-400945 (pIC_{50} 8.6) [397]

STE7 family

Enzymes → Kinases (EC 2.7.x.x) → STE: Homologs of yeast Sterile 7, Sterile 11, Sterile 20 kinases → STE7 family

Nomenclature	mitogen-activated protein kinase kinase 1	mitogen-activated protein kinase kinase 2
Common abbreviation	MEK1	MEK2
HGNC, UniProt	*MAP2K1*, Q02750	*MAP2K2*, P36507
EC number	2.7.12.2	2.7.12.2
Inhibitors	trametinib (pIC_{50} 9–9.1) [206, 659], PD 0325901 (pIC_{50} 8.1) [243]	trametinib (pIC_{50} 8.7) [659]
Allosteric modulators	binimetinib (Negative) (pIC_{50} 7.9) [468], refametinib (Negative) (pIC_{50} 7.7) [281], CI-1040 (Negative) (pK_d 6.9) [130]	binimetinib (Negative) (pIC_{50} 7.9) [468], refametinib (Negative) (pIC_{50} 7.3) [281]
Selective allosteric modulators	cobimetinib (Negative) (pIC_{50} 9.1) [500]	–

Abl family

Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Non-receptor tyrosine kinases (nRTKs) → Abl family

Nomenclature	ABL proto-oncogene 1, non-receptor tyrosine kinase
Common abbreviation	Abl
HGNC, UniProt	*ABL1*, P00519
EC number	2.7.10.2
Inhibitors	compound 8h (pIC_{50} 9.7) [596], dasatinib (pIC_{50} 9.6) [314], compound 24 (pIC_{50} 9.3) [136], PD-173955 (pK_d 9.2) [130], bosutinib (pIC_{50} 9) [210], PD-173955 (pIC_{50} ~8.3) [427], bafetinib (pIC_{50} 7.6–8.2) [264, 319], ponatinib (pIC_{50} 8.1) [269], nilotinib (pIC_{50} 7.8) [439], PP121 (pIC_{50} 7.7) [18], imatinib (pIC_{50} 6.7) [264], GNF-5 (pIC_{50} 6.7) [673]

Ack family

Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Non-receptor tyrosine kinases (nRTKs) → Ack family

Nomenclature	tyrosine kinase non receptor 2
Common abbreviation	Ack
HGNC, UniProt	*TNK2*, Q07912
EC number	2.7.10.2
Inhibitors	compound 30 (pIC_{50} 9) [143]

Janus kinase (JakA) family

Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Non-receptor tyrosine kinases (nRTKs) → Janus kinase (JakA) family

Overview: Janus kinases (JAKs) are a fam.ily of four enzymes; JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). They are essential for cytokine signalling and are strongly linked to both cancer and inflammatory diseases.

Nomenclature	Janus kinase 1	Janus kinase 2	Janus kinase 3	tyrosine kinase 2
Common abbreviation	JAK1	JAK2	JAK3	Tyk2
HGNC, UniProt	*JAK1*, P23458	*JAK2*, O60674	*JAK3*, P52333	*TYK2*, P29597
EC number	2.7.10.2	2.7.10.2	2.7.10.2	2.7.10.2
Inhibitors	ruxolitinib (pIC_{50} 8.5–10.1) [236, 483], filgotinib (pIC_{50} 8) [608]	ilginatinib (pIC_{50} 9.1) [431], BMS-911543 (pIC_{50} 9) [480], AT-9283 (pIC_{50} 8.9) [266], XL019 (pIC_{50} 8.7) [176], fedratinib (pIC_{50} 8.5) [389, 638], gandotinib (pIC_{50} 8.4) [385]	AT-9283 (pIC_{50} 9) [266]	–
Selective inhibitors	–	compound 1d (pIC_{50} >9) [624]	–	–
Comments	–	The $JAK2^{V617F}$ mutation, which causes constitutive activation, plays an oncogenic role in the pathogenesis of the myeloproliferative disorders, polycythemia vera, essential thrombocythemia, and idiopathic myelofibrosis [74, 133]. Small molecule compounds which inhibit aberrant JAK2 activity are being developed as novel anti-cancer pharmaceuticals.	–	–

Src family

Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Non-receptor tyrosine kinases (nRTKs) → Src family

Overview: Activation of Src-family kinases leads to both stimulatory and inhibitory signaling responses, with cell-specific and signaling pathway-specific outcomes and redundancy of kinase function.

Immune system:
In immune cells Src kinases are involved in many signalling pathways, including ITAM- and ITIM-domain-containing receptor signaling, integrin signaling, and responses to chemokines/chemoattractants, cytokines, innate immune stimuli and a large variety of non-immune cell specific stimuli (UV irradiation, heat, osmotic shock *etc.*). In many cases Src kinases signal to MAP kinase or NF-κB pathways, but they can also modulate other pathways through less well characterized mechanisms.

The primary T cell Src kinases are Lck and Fyn; the main B cell Srcs are Lyn, Fyn and Blk. Mast cells express Fyn and Lyn, with low expression of Src.

Nomenclature	BLK proto-oncogene, Src family tyrosine kinase	fyn related Src family tyrosine kinase	FYN proto-oncogene, Src family tyrosine kinase	LYN proto-oncogene, Src family tyrosine kinase	SRC proto-oncogene, non-receptor tyrosine kinase
Common abbreviation	Blk	FRK	Fyn	Lyn	Src
HGNC, UniProt	*BLK*, P51451	*FRK*, P42685	*FYN*, P06241	*LYN*, P07948	*SRC*, P12931
EC number	2.7.10.2	2.7.10.2	2.7.10.2	2.7.10.2	2.7.10.2
Inhibitors	–	–	PP1 (pIC_{50} 8.2) [239]	bafetinib (pIC_{50} 8) [264]	WH-4-023 (pIC_{50} 8.2) [394], PD166285 (pK_i 8.1) [458], PP121 (pIC_{50} 7.8) [18], ENMD-2076 (pIC_{50} 7.7) [476]

Tec family

Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Non-receptor tyrosine kinases (nRTKs) → Tec family

Nomenclature	BMX non-receptor tyrosine kinase	Bruton tyrosine kinase	TXK tyrosine kinase
Common abbreviation	Etk	Btk	TXK
HGNC, UniProt	*BMX*, P51813	*BTK*, Q06187	*TXK*, P42681
EC number	2.7.10.2	2.7.10.2	2.7.10.2
Inhibitors	compound 38 (pIC_{50} 9.1) [347], ibrutinib (pIC_{50} 9.1) [371], compound 31 (pIC_{50} 8.7) [347]	ibrutinib (pIC_{50} 9.3) [457], compound 31 (pIC_{50} 8.4) [347], compound 38 (pIC_{50} >8.4) [347]	–
Selective inhibitors	BMX-IN-1 (pIC_{50} 8.1) [358]	CGI1746 (pIC_{50} 8.7) [140], CHMFL-BTK-11 (Irreversible inhibition) (pIC_{50} 7.6) [649]	–

RAF family

Enzymes → Kinases (EC 2.7.x.x) → TKL: Tyrosine kinase-like → RAF family

Nomenclature	B-Raf proto-oncogene, serine/threonine kinase	Raf-1 proto-oncogene, serine/threonine kinase
Common abbreviation	B-Raf	c-Raf
HGNC, UniProt	*BRAF*, P15056	*RAF1*, P04049
EC number	2.7.11.1	2.7.11.1
Inhibitors	GDC-0879 (pIC_{50} 9.7–9.9) [130, 240], dabrafenib (pIC_{50} 8.5) [337], regorafenib (pIC_{50} 7.6) [670], vemurafenib (pIC_{50} 7) [625], PLX-4720 (pK_d 6.5) [130], compound 2 (pK_d 6.3) [263], CHIR-265 (pK_d 5.9) [130]	–
Selective inhibitors	–	GW5074 (pIC_{50} 8.1) [101]

Further reading on Kinases (EC 2.7.x.x)

Eglen R *et al.* (2011) Drug discovery and the human kinome: recent trends. *Pharmacol. Ther.* **130**: 144-56 [PMID:21256157]

Graves LM *et al.* (2013) The dynamic nature of the kinome. *Biochem. J.* **450**: 1-8 [PMID:23343193]

Liu Q *et al.* (2013) Developing irreversible inhibitors of the protein kinase cysteinome. *Chem. Biol.* **20**: 146-59 [PMID:23438744]

Martin KJ *et al.* (2012) Selective kinase inhibitors as tools for neuroscience research. *Neuropharmacology* **63**: 1227-37 [PMID:22846224]

Tarrant MK *et al.* (2009) The chemical biology of protein phosphorylation. *Annu. Rev. Biochem.* **78**: 797-825 [PMID:19489734]

Wu-Zhang AX *et al.* (2013) Protein kinase C pharmacology: refining the toolbox. *Biochem. J.* **452**: 195-209 [PMID:23662807]

Lanosterol biosynthesis pathway

Enzymes → Lanosterol biosynthesis pathway

Overview: Lanosterol is a precursor for cholesterol, which is synthesized primarily in the liver in a pathway often described as the mevalonate or HMG-CoA reductase pathway. The first two steps (formation of acetoacetyl CoA and the mitochondrial generation of (S)-3-hydroxy-3-methylglutaryl-CoA) are also associated with oxidation of fatty acids.

Nomenclature	acetyl-CoA acetyltransferase 1	acetyl-CoA acetyltransferase 2	hydroxymethylglutaryl-CoA synthase 1	hydroxymethylglutaryl-CoA synthase 2
HGNC, UniProt	*ACAT1*, P24752	*ACAT2*, Q9BWD1	*HMGCS1*, Q01581	*HMGCS2*, P54868
EC number	2.3.1.9: 2acetyl CoA = acetoacetyl CoA + coenzyme A	2.3.1.9: 2acetyl CoA = acetoacetyl CoA + coenzyme A	2.3.3.10: acetyl CoA + H_2O + acetoacetyl CoA -> (S)-3-hydroxy-3-methylglutaryl-CoA + coenzyme A	2.3.3.10: acetyl CoA + H_2O + acetoacetyl CoA -> (S)-3-hydroxy-3-methylglutaryl-CoA + coenzyme A
Comments	–	–	HMGCoA synthase is found in cytosolic (HMGCoA synthase 1) and mitochondrial (HMGCoA synthase 2) versions; the former associated with (R)-mevalonate synthesis and the latter with ketogenesis.	

Nomenclature	hydroxymethylglutaryl-CoA reductase
HGNC, UniProt	*HMGCR*, P04035
EC number	1.1.1.34: (S)-3-hydroxy-3-methylglutaryl-CoA + NADPH -> (R)-mevalonate + coenzyme A + $NADP^+$ Reaction mechanism:: **First step:** (S)-3-hydroxy-3-methylglutaryl-CoA + NADPH -> mevaldyl-CoA + $NADP^+$ **Second step:** mevaldyl-CoA + H2O -> (R)-mevalonate + $NADP^+$
Inhibitors	lovastatin (Competitive) (pK_i 9.2) [12], rosuvastatin (Competitive) (pIC_{50} 8.3) [280], cerivastatin (Competitive) (pK_i 8.2) [77], atorvastatin (Competitive) (pIC_{50} 8.1) [280], cerivastatin (Competitive) (pIC_{50} 8) [595], simvastatin (Competitive) (pIC_{50} 8) [280], fluvastatin (Competitive) (pIC_{50} 7.6) [280]
Comments	HMGCoA reductase is associated with intracellular membranes; enzymatic activity is inhibited by phosphorylation by AMP-activated kinase. The enzymatic reaction is a three-step reaction involving the intermediate generation of mevaldehyde-CoA and mevaldehyde.

Nomenclature	mevalonate kinase	phosphomevalonate kinase	diphosphomevalonate decarboxylase
HGNC, UniProt	*MVK*, Q03426	*PMVK*, Q15126	*MVD*, P53602
EC number	2.7.1.36: ATP + (R)-mevalonate -> ADP + (R)-5-phosphomevalonate	2.7.4.2: ATP + (R)-5-phosphomevalonate = ADP + (R)-5-diphosphomevalonate	4.1.1.33: ATP + (R)-5-diphosphomevalonate -> ADP + isopentenyl diphosphate + CO_2 + PO_3^{4-}
Comments	Mevalonate kinase activity is regulated by the downstream products farnesyl diphosphate and geranyl diphosphate as an example of feedback inhibition.	–	–

Nomenclature	isopentenyl-diphosphate Δ-isomerase 1	isopentenyl-diphosphate Δ-isomerase 2	geranylgeranyl diphosphate synthase
HGNC, UniProt	*IDI1*, Q13907	*IDI2*, Q9BXS1	*GGPS1*, O95749
EC number	5.3.3.2: isopentenyl diphosphate = dimethylallyl diphosphate	5.3.3.2: isopentenyl diphosphate = dimethylallyl diphosphate	2.5.1.29: trans,trans-farnesyl diphosphate + isopentenyl diphosphate -> geranylgeranyl diphosphate + diphosphate 2.5.1.10: geranyl diphosphate + isopentenyl diphosphate -> trans,trans-farnesyl diphosphate + diphosphate 2.5.1.1: dimethylallyl diphosphate + isopentenyl diphosphate = geranyl diphosphate + diphosphate

Nomenclature	farnesyl diphosphate synthase	squalene synthase	squalene monooxygenase	lanosterol synthase
HGNC, UniProt	*FDPS*, P14324	*FDFT1*, P37268	*SQLE*, Q14534	*LSS*, P48449
EC number	2.5.1.10: geranyl diphosphate + isopentenyl diphosphate -> trans,trans-farnesyl diphosphate + diphosphate 2.5.1.1: dimethylallyl diphosphate + isopentenyl diphosphate = geranyl diphosphate + diphosphate	2.5.1.21: 2trans,trans-farnesyl diphosphate -> presqualene diphosphate + diphosphate presqualene diphosphate + NAD(P)H + H^+ -> squalene + diphosphate + $NAD(P)^+$	1.14.13.132: H^+ + NADPH + O_2 + squalene = H_2O + $NADP^+$ + (*S*)-2,3-epoxysqualene	5.4.99.7: (*S*)-2,3-epoxysqualene = lanosterol
Cofactors	–	NADPH	–	–
Inhibitors	risedronate (pIC_{50} 8.4) [43], zoledronic acid (pK_i 7.1) [153], alendronate (pIC_{50} 6.3) [43]	zaragozic acid A (pK_i 10.1) [44] – Rat, zaragozic acid A (pIC_{50} 9.2) [597]	–	–
Selective inhibitors	ibandronic acid (pK_i 6.7) [153], pamidronic acid (pIC_{50} 6.7) [153]	–	–	–

Further reading on Lanosterol biosynthesis pathway

Moutinho M *et al.* (2017) The mevalonate pathway in neurons: It's not just about cholesterol. *Exp. Cell Res.* **360**: 55-60 [PMID:28232115]

Mullen PJ *et al.* (2016) The interplay between cell signalling and the mevalonate pathway in cancer. *Nat. Rev. Cancer* **16**: 718-731 [PMID:27562463]

Ness GC. (2015) Physiological feedback regulation of cholesterol biosynthesis: Role of translational control of hepatic HMG-CoA reductase and possible involvement of oxylanosterols. *Biochim. Biophys. Acta* **1851**: 667-73 [PMID:25701719]

Porter TD. (2015) Electron Transfer Pathways in Cholesterol Synthesis. *Lipids* **50**: 927-36 [PMID:26344922]

Samaras K *et al.* (2016) Does statin use cause memory decline in the elderly? *Trends Cardiovasc. Med.* **26**: 550-65 [PMID:27177529]

Nucleoside synthesis and metabolism

Enzymes → Nucleoside synthesis and metabolism

Overview: The *de novo* synthesis and salvage of nucleosides have been targetted for therapeutic advantage in the treatment of particular cancers and gout. Dihydrofolate reductase produces tetrahydrofolate, a cofactor required for synthesis of purines, pyrimidines and amino acids. GART allows formylation of phosphoribosylglycinamide, an early step in purine biosynthesis. Dihydroorotate dehydrogenase produces orotate, a key intermediate in pyrimidine synthesis. IMP dehydrogenase generates xanthosine monophosphate, an intermediate in GTP synthesis.

Nomenclature	dihydrofolate reductase	phosphoribosylglycinamide formyltransferase, phosphoribosylglycinamide synthetase, phosphoribosylaminoimidazole synthetase	dihydroorotate dehydrogenase (quinone)	inosine monophosphate dehydrogenase 1	inosine monophosphate dehydrogenase 2	thymidylate synthetase
Common abbreviation	DHFR	GART	DHODH	IMPDH1	IMPDH2	TYMS
HGNC, UniProt	*DHFR*, P00374	*GART*, P22102	*DHODH*, Q02127	*IMPDH1*, P20839	*IMPDH2*, P12268	*TYMS*, P04818
EC number	1.5.1.3	2.1.2.2 6.3.3.1 6.3.4.13	1.3.5.2	1.1.1.205	1.1.1.205	2.1.1.45
Inhibitors	–	pemetrexed (pK_i 5) [540] – Mouse	teriflunomide (pK_i 7.5) [253]	mycophenolic acid (pIC_{50} 7.7) [433]	mycophenolic acid (pIC_{50} 7.7) [433]	–
Selective inhibitors	methotrexate (pK_i 8.9) [511]	–	–	–	–	raltitrexed (pIC_{50} 6.5) [194]

Nomenclature	purine nucleoside phosphorylase	xanthine dehydrogenase	ribonucleotide reductase catalytic subunit M1	ribonucleotide reductase regulatory subunit M2	ribonucleotide reductase regulatory TP53 inducible subunit M2B
Common abbreviation	PNP	XDH	ribonucleotide reductase M1	ribonucleotide reductase M2	ribonucleotide reductase M2B (TP53 inducible)
HGNC, UniProt	*PNP*, P00491	*XDH*, P47989	*RRM1*, P23921	*RRM2*, P31350	*RRM2B*, Q7LG56
EC number	1.4.2.1 Purine-nucleoside phosphorylase: Purine nucleoside + phosphate <=> purine + alpha-D-ribose 1-phosphate Purine deoxynucleoside + phosphate <=> purine + 2'-deoxy-alpha-D-ribose 1-phosphate	1.17.1.4	1.17.14.1	1.17.4.1	1.17.1.4
Inhibitors	–	febuxostat (pIC_{50} 8.9) [162]	–	–	–

Comments: TYMS allows the interconversion of dUMP and dTMP, thereby acting as a crucial step in DNA synthesis. PNP allows separation of a nucleoside into the nucleobase and ribose phosphate for nucleotide salvage. XDH generates urate in the purine degradation pathway. Post-translational modifications of XDH convert the enzymatic reaction to a xanthine oxidase, allowing the interconversion of hypoxanthine and xanthine, with the production (or consumption) of reactive oxygen species.

Further reading on Nucleoside synthesis and metabolism

Day RO *et al.* (2016) Xanthine oxidoreductase and its inhibitors: relevance for gout. *Clin Sci (Lond).* **130**: 2167-2180 [PMID:27798228]

Okafor ON *et al.* (2017) Allopurinol as a therapeutic option in cardiovascular disease. *Pharmacol Ther.* **172**: 139-150 [PMID:27916655]

Paraoxonase (PON) family

Enzymes → Paraoxonase (PON) family

Overview: Paraoxonases (PON) are calcium-dependent esterases, which may be involved in lipoprotein turnover and the conversion of lactone statin prodrugs, as well as being targets of organophosphates, such as the insecticide paraoxon.

Nomenclature	paraoxonase 1	paraoxonase 2	paraoxonase 3
Common abbreviation	PON1	PON2	PON3
HGNC, UniProt	*PON1*, P27169	*PON2*, Q15165	*PON3*, Q15166
EC number	3.1.8.1 An aryl dialkyl phosphate + H(2)O <=> dialkyl phosphate + an aryl alcohol 3.1.1.2 A phenyl acetate + H(2)O <=> a phenol + acetate 3.1.1.81 An N-acyl-L-homoserine lactone + H(2)O <=> an N-acyl-L-homoserine	3.1.1.2 A phenyl acetate + H(2)O <=> a phenol + acetate 3.1.1.81 A N-acyl-L-homoserine lactone + H(2)O <=> a N-acyl-L-homoserine	3.1.8.1 An aryl dialkyl phosphate + H(2)O <=> dialkyl phosphate + an aryl alcohol 3.1.1.2 A phenyl acetate + H(2)O <=> a phenol + acetate 3.1.1.81 A N-acyl-L-homoserine lactone + H(2)O <=> a N-acyl-L-homoserine
Comments	PON1 forms homodimers. Loss-of-function mutations in PON1 are associated with microvascular complications of diabetes [303, 304].	PON2 forms heterotrimers [150].	PON3 likely forms heterodimers *in vivo* [150].

Further reading on Paraoxonase

Dardiotis E *et al.* (2019) Paraoxonase-1 genetic polymorphisms in organophosphate metabolism. *Toxicology.* **411**: 24-31 [PMID:30359673]

Lioudaki S *et al.* (2019) Paraoxonase-1: Characteristics and Role in Atherosclerosis and Carotid Artery Disease. *Curr Vasc Pharmacol.* **17**: 141-146 [PMID:29189170]

Peptidases and proteinases

Enzymes → Peptidases and proteinases

Overview: Peptidases and proteinases hydrolyse peptide bonds, and can be simply divided on the basis of whether terminal peptide bonds are cleaved (exopeptidases and exoproteinases) at the amino terminus (aminopeptidases) or carboxy terminus (carboxypeptidases). Non-terminal peptide bonds are cleaved by endopeptidases and endoproteinases, which are divided into serine endopeptidases (EC 3.4.21.-), cysteine endopeptidases (EC 3.4.22.-), aspartate endopeptidases (EC 3.4.23.-), metalloendopeptidases (EC 3.4.24.-) and threonine endopeptidases (EC 3.4.25.-).
Since it is beyond the scope of the Guide to list all peptidase and proteinase activities, this summary focuses on selected enzymes of significant pharmacological interest that have ligands (mostly small-molecules) directed against them. For those interested in detailed background we recommend the MEROPS database [493] (with whom we collaborate) as an information resource [494].

A1: Pepsin

Enzymes → Peptidases and proteinases → AA: Aspartic (A) Peptidases → A1: Pepsin

Nomenclature	renin
HGNC, UniProt	*REN*, P00797
EC number	3.4.23.15
Inhibitors	aliskiren (pIC_{50} 9.2) [655]

A22: Presenilin

Enzymes → Peptidases and proteinases → AD: Aspartic (A) Peptidases → A22: Presenilin

Overview: Presenilin (PS)-1 or -2 act as the catalytic component/essential co-factor of the γ-secretase complex responsible for the final carboxy-terminal cleavage of amyloid precursor protein (APP) [302] in the generation of amyloid beta (Aβ) [9, 579]. Given that the accumulation and aggregation of Aβ in the brain is pivotal in the development of Alzheimer's disease (AD), inhibition of PS activity is one mechanism being investigated as a therapeutic option for AD [211]. Several small molecule inhibitors of PS-1 have been investigated, with some reaching early clinical trials, but none have been formally approved. Dewji *et al.* (2015) have reported that small peptide fragments of human PS-1 can significantly inhibit Aβ production (total Aβ, Aβ40 and Aβ42) both *in vitro* and when infused in to the brains of APP transgenic mice [139]. The most active small peptides in this report were P4 and P8, from the amino-terminal domain of PS-1.

Information on members of this family may be found in the online database.

C14: Caspase

Enzymes → Peptidases and proteinases → CD: Cysteine (C) Peptidases → C14: Caspase

Overview: Caspases, (E.C. 3.4.22.-) which derive their name from Cysteine ASPartate-specific proteASES, include at least two families; initiator caspases (caspases 2, 8, 9 and 10), which are able to hydrolyse and activate a second family of effector caspases (caspases 3, 6 and 7), which themselves are able to hydrolyse further cellular proteins to bring about programmed cell death. Caspases are heterotetrameric, being made up of two pairs of subunits, generated by a single gene product, which is proteolysed to form the mature protein. Members of the mammalian inhibitors of apoptosis proteins (IAP) are able to bind the procaspases, thereby preventing maturation to active proteinases.

Information on members of this family may be found in the online database.

Comments: CARD16 (Caspase recruitment domain-containing protein 16, caspase-1 inhibitor COP, CARD only domain-containing protein 1, pseudo interleukin-1β converting enzyme, pseudo-ICE, ENSG00000204397) shares sequence similarity with some of the caspases.

M1: Aminopeptidase N

Enzymes → Peptidases and proteinases → MA: Metallo (M) Peptidases → M1: Aminopeptidase N

Overview: Aminopeptidases catalyze the cleavage of amino acids from the amino (N) terminus of protein or peptide substrates, and are involved in many essential cellular functions. Members of this enzyme family may be monomeric or multi-subunit complexes, and many are zinc metalloenzymes [590].

Nomenclature	Leukotriene A_4 hydrolase
HGNC, UniProt	*LTA4H*, P09960
EC number	3.3.2.6
Inhibitors	bestatin (pK_i 5.4) [450]

M2: Angiotensin-converting (ACE and ACE2)

Enzymes → Peptidases and proteinases → MA: Metallo (M) Peptidases → M2: Angiotensin-converting (ACE and ACE2)

Nomenclature	Angiotensin-converting enzyme
Common abbreviation	ACE
HGNC, UniProt	*ACE*, P12821
EC number	3.4.15.1
Substrates	Ac-SDKP
Endogenous substrates	angiotensin I (*AGT*, P01019) > angiotensin II (*AGT*, P01019)
Inhibitors	zofenoprilat (pK_i 9.4) [329] – Rabbit, captopril (pK_i 8.4) [410], zofenopril
Selective inhibitors	perindoprilat (pIC_{50} 9) [83], cilazaprilat (pIC_{50} 8.7) [630] – Rabbit, imidaprilat (pIC_{50} 8.7) [507], lisinopril-tryptophan (C-domain assay) (pIC_{50} 8.2) [631], RXP-407 (N-domain selective inhibition) (pIC_{50} 8.1) [538], fosinoprilat (pIC_{50} 8) [131] – Rabbit, enalaprilat (pIC_{50} 7.5) [98], benazeprilat (pIC_{50} 6.6) [342]
Comments	Reports of ACE GPI hydrolase activity [322] have been refuted [344]

M10: Matrix metallopeptidase

Enzymes → Peptidases and proteinases → MA: Metallo (M) Peptidases → M10: Matrix metallopeptidase

Overview: Matrix metalloproteinases (MMP) are calcium- and zinc-dependent proteinases regulating the extracellular matrix and are often divided (*e.g.* [614]) on functional and structural bases into gelatinases, collagenases, stromyelinases and matrilysins, as well as membrane type-MMP (MT-MMP).

Nomenclature	MMP2	MMP8
HGNC, UniProt	*MMP2*, P08253	*MMP8*, P22894
EC number	3.4.24.24	3.4.24.34
Selective inhibitors	ARP100 [603]	–
Comments	MMP2 is categorised as a gelatinase with substrate specificity for gelatinase A.	MMP8 is categorised as a collagenase.

Comments: A number of small molecule 'broad spectrum' inhibitors of MMP have been described, including marimastat and batimastat.
Tissue inhibitors of metalloproteinase (TIMP) proteins are endogenous inhibitors acting to chelate MMP proteins: TIMP1 (*TIMP1*, P01033), TIMP2 (*TIMP2*, P16035), TIMP3 (*TIMP3*, P35625), TIMP4 (*TIMP4*, Q99727)

M12: Astacin/Adamalysin

Enzymes → Peptidases and proteinases → MA: Metallo (M) Peptidases → M12: Astacin/Adamalysin

Overview: ADAM (A Disintegrin And Metalloproteinase domain containing proteins) metalloproteinases cleave cell-surface or transmembrane proteins to generate soluble and membrane-limited products.
ADAMTS (with thrombospondin motifs) metalloproteinases cleave cell-surface or transmembrane proteins to generate soluble and membrane-limited products.

Information on members of this family may be found in the online database.

Comments: Additional ADAM family members include AC123767.2 (cDNA FLJ58962, moderately similar to mouse ADAM3, ENSG00000231168), AL160191.3 (ADAM21-like protein, ENSG00000235812), AC136428.3-2 (ENSG00000185520) and ADAMDEC1 (decysin 1, ENSG00000134028).
Other ADAMTS family members include AC104758.12-5 (FLJ00317 protein Fragment ENSG00000231463), AC139425.3-1 (ENSG00000225577), and AC126339.6-1 (ENSG00000225734).

M28: Aminopeptidase Y

Enzymes → Peptidases and proteinases → MH: Metallo (M) Peptidases → M28: Aminopeptidase Y

Nomenclature	Folate hydrolase (prostate-specific membrane antigen) 1
HGNC, UniProt	*FOLH1*, Q04609
EC number	3.4.17.21
Antibodies	capromab (Binding)
Comments	Folate hydrolase is also known as NAALADase as it is responsible for the hydrolysis of N-acetaspartylglutamate to form N-acetylaspartate and L-glutamate (L-glutamic acid). In the gut, the enzyme assists in the assimilation of folate by hydrolysing dietary poly-gamma-glutamylfolate. The enzyme is highly expressed in the prostate, and its expression is up-regulated in cancerous tissue. A tagged version of the antibody capromab has been used for imaging purposes.

Comments: Folate hydrolase is also known as NAALADase as it is responsible for the hydrolysis of N-acetaspartylglutamate to form N-acetylaspartate and L-glutamate. In the gut, the enzyme assists in the assimilation of folate by hydrolysing dietary poly-gamma-glutamylfolate. The enzyme is highly expressed in the prostate, and its expression is up-regulated in cancerous tissue. A tagged version of the antibody capromab has been used for imaging purposes.

M19: Membrane dipeptidase

Enzymes → Peptidases and proteinases → MJ: Metallo (M) Peptidases → M19: Membrane dipeptidase

Nomenclature	Dipeptidase 1
HGNC, UniProt	*DPEP1*, P16444
EC number	3.4.13.19: $LTD_4 + H_2O = LTE_4 + glycine$
Inhibitors	cilastatin (pK_i 6) [215]

S1: Chymotrypsin

Enzymes → Peptidases and proteinases → PA: Serine (S) Peptidases → S1: Chymotrypsin

Nomenclature	complement C1r	coagulation factor II, thrombin	coagulation factor X
HGNC, UniProt	*C1R*, P00736	*F2*, P00734	*F10*, P00742
EC number	3.4.21.41	3.4.21.5	3.4.21.6
Inhibitors	nafamostat (pIC_{50} 4.9) [251]	lepirudin (pK_i 13) [626], desirudin (pK_i 12.7) [293], AZ12971554 (pK_i 9.5) [21], melagatran (pK_i 8.7) [228], bivalirudin (pK_i 8.6) [646], dabigatran (pK_i 8.3) [246], argatroban (pK_i 7.7) [276]	apixaban (pK_i 10.1) [647], rivaroxaban (pK_i 9.4) [466], edoxaban (pK_i 9.2) [471]
Selective inhibitors	–	Dup-714 (pK_i 10.4) [192], AR-H067637 (pIC_{50} 8.4) [132]	–

Nomenclature	elastase, neutrophil expressed	plasminogen	plasminogen activator, tissue type	serine protease 1	tryptase alpha/beta 1
HGNC, UniProt	*ELANE*, P08246	*PLG*, P00747	*PLAT*, P00750	*PRSS1*, P07477	*TPSAB1*, Q15661
EC number	3.4.21.37	3.4.21.7	3.4.21.68	3.4.21.4	3.4.21.59
Inhibitors	alvelestat (pK_i 8) [568], sivelestat (pIC_{50} 7.4) [119]	aprotinin {Bovine} (Binding) (pIC_{50} 6.8) [560], tranexamic acid (Binding) (pIC_{50} 3.6) [560]	–	nafamostat (pIC_{50} 7.8) [251]	nafamostat (pIC_{50} 10) [422]
Selective inhibitors	–	6-aminocaproic acid (Binding) (pIC_{50} 4.4) [97]	–	–	gabexate (pIC_{50} 8.5) [159]

T1: Proteasome

Enzymes → Peptidases and proteinases → PB: Threonine (T) Peptidases → T1: Proteasome

Overview: The T1 macropain beta subunits form the catalytic proteinase core of the 20S proteasome complex [106]. This catalytic core enables the degradation of peptides with Arg, Phe, Tyr, Leu, and Glu adjacent to the cleavage site. The β5 subunit is the principal target of the approved drug proteasome inhibitor bortezomib.

Nomenclature	proteasome subunit beta 5
HGNC, UniProt	*PSMB5*, P28074
EC number	3.4.25.1
Inhibitors	bortezomib (pIC_{50} 7.7) [428]
Selective inhibitors	ixazomib (pK_i 9) [332]

S8: Subtilisin

Enzymes → Peptidases and proteinases → SB: Serine (S) Peptidases → S8: Subtilisin

Overview: One member of this family has garnered intense interest as a clinical drug target. As liver PCSK9 acts to maintain cholesterol homeostasis, it has become a target of intense interest for clinical drug development. Inhibition of PCSK9 can lower low-density cholesterol (LDL-C) by clearing LDLR-bound LDL particles, thereby lowering circulating cholesterol levels. It is hypothesised that this action may improve outcomes in patients with atherosclerotic cardiovascular disease [368, 516, 567]. Therapeutics which inhibit PCSK9 are viewed as potentially lucrative replacements for statins, upon statin patent expiry. Several monoclonal antibodies including alirocumab, evolocumab, bococizumab, RG-7652 and LY3015014 are under development. One RNAi therapeutic, code named ALN-PCS02, is also in development [123, 173, 180].

Information on members of this family may be found in the online database.

S9: Prolyl oligopeptidase

Enzymes → Peptidases and proteinases → SC: Serine (S) Peptidases → S9: Prolyl oligopeptidase

Nomenclature	dipeptidyl peptidase 4
HGNC, UniProt	*DPP4*, P27487
EC number	3.4.14.5
Endogenous substrates	glucagon-like peptide 1 (*GCG*, P01275)
Inhibitors	saxagliptin (pK_i 9.2) [226], linagliptin (pK_i 9) [155], sitagliptin (pIC_{50} 8.1) [129], vildagliptin (pK_i 7.8) [226]
Selective inhibitors	ZY15557 (Competitive) (pK_i 8.3) [285]

Poly ADP-ribose polymerases

Enzymes → Poly ADP-ribose polymerases

Overview: The Poly ADP-ribose polymerase family is a series of enzymes, where the best characterised members are nuclear proteins which are thought to function by binding to single strand breaks in DNA, allowing the recruitment of repair enzymes by the synthesis of NAD-derived ADP-ribose polymers, which are subsequently degraded by a glycohydrolase (*PARG*, Q86W56).

Nomenclature	poly(ADP-ribose) polymerase 1	poly(ADP-ribose) polymerase 2	poly (ADP-ribose) polymerase 3
Common abbreviation	PARP1	PARP2	PARP3
HGNC, UniProt	*PARP1*, P09874	*PARP2*, Q9UGN5	*PARP3*, Q9Y6F1
EC number	2.4.2.30	2.4.2.30	–

Further reading on Poly ADP-ribose polymerases

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Zeniou M *et al.* (2019) Therapeutic considerations of PARP in stem cell biology: Relevance in cancer and beyond. *Biochem Pharmacol* [PMID:31202733]

Prolyl hydroxylases

Enzymes → Prolyl hydroxylases

Overview: Hypoxia-inducible factors (HIFs) are rapidly-responding sensors of reductions in local oxygen tensions, prompting changes in gene transcription. Listed here are the 4-prolyl hydroxylase family, members of which have been identified to hydroxylate proline residues in HIF1α (*HIF1A*; Q16665) leading to an increased degradation through proteasomal hydrolysis. This action requires molecular oxygen and 2-oxoglutarate, and so reduced oxygen tensions prevents HIF1α hydroxylation, allowing its translocation to the nucleus and dimerisation with HIF1β (also known as *ARNT*; P27540), thereby allowing interaction with the genome as a transcription factor.

Nomenclature	egl-9 family hypoxia inducible factor 2	egl-9 family hypoxia inducible factor 1	egl-9 family hypoxia inducible factor 3
Common abbreviation	PHD1	PHD2	PHD3
HGNC, UniProt	*EGLN2*, Q96KS0	*EGLN1*, Q9GZT9	*EGLN3*, Q9H6Z9
EC number	1.14.11.29	1.14.11.29	1.14.11.29

Further reading on Prolyl hydroxylases

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Lanigan SM and O'Connor JJ. (2019) Prolyl hydroxylase domain inhibitors: can multiple mechanisms be an opportunity for ischemic stroke? *Neuropharmacology* **148**: 117-130 [PMID:30578795]
Singh L *et al.* (2018) Prolyl hydroxylase 2: a promising target to inhibit hypoxia-induced cellular metabolism in cancer cells. *Drug Discov Today* **23**: 1873-1882 [PMID:29772209]
Vasta JD and Raines RT *et al.* (2018) Collagen Prolyl 4-Hydroxylase as a Therapeutic Target. *J Med Chem* **61**: 10403-10411 [PMID:29986141]
Watts ER and Walmsley SR. (2019) Inflammation and Hypoxia: HIF and PHD Isoform Selectivity. *Trends Mol Med* **25**: 33-46 [PMID:30442494]

Sphingosine 1-phosphate turnover

Enzymes → Sphingosine 1-phosphate turnover

Overview: S1P (sphingosine 1-phosphate) is a bioactive lipid which, after release from cells via certain transporters, acts as a ligand for a family of five S1P-specific G protein-coupled receptors (S1P1-5). However, it also has a number of intracellular targets. S1P is formed by the ATP-dependent phosphorylation of sphingosine, catalysed by two isoforms of sphingosine kinase (EC 2.7.1.91). It can be dephosphorylated back to sphingosine by sphingosine 1-phosphate phosphatase (EC 3.1.3) or cleaved into phosphoethanolamine and hexadecenal by sphingosine 1-phosphate lyase (EC 4.1.2.27). Recessive mutations in the S1P lyase (SPL) gene underlie a recently identified sphingolipidosis: SPL Insufficiency Syndrome (SPLIS). In general, S1P promotes cell survival, proliferation, migration, adhesion and inhibition of apoptosis. Intracellular S1P affects epigenetic regulation, endosomal processing, mitochondrial function and cell proliferation/senescence. S1P has myriad physiological functions, including vascular development, lymphocyte trafficking and neurogenesis. However, S1P is also involved in a number of diseases such as cancer, inflammation and fibrosis. Therefore, its GPCRs and enzymes of synthesis and degradation are a major focus for drug discovery.

Sphingosine kinase

Enzymes → Sphingosine 1-phosphate turnover → Sphingosine kinase

Overview: SPHK1 and SPHK2 are encoded by different genes with some redundancy of function; genetic deletion of both Sphk1 and Sphk2, but not either alone, is embryonic lethal in mice. There are splice variants of each isoform (SphK1a-c and SphK2a, b), distinguished by their N-terminal sequences. SPHK1 and SPHK2 differ in tissue distribution, sub-cellular localisation, biochemical properties and regulation. They regulate discrete pools of S1P. Receptor stimulation induces SPHK1 translocation from the cytoplasm to the plasma membrane. SPHK1 translocation is regulated by phosphorylation/dephosphorylation, specific protein:protein interactions and interaction with specific lipids at the plasma membrane. SPHK1 is a dimeric protein, as confirmed by its crystal structure which forms a positive cluster, between protomers, essential for interaction with anionic phospholipids in the plasma membrane. SPHK2 is localised to the ER or associated with mitochondria or shuttles in/out of the nucleus, regulated by phosphorylation. Intracellular targets of nuclear S1P include the catalytic subunit of telomerase (TERT) and regulators of gene expression including histone deacetylases (HDAC 1/2) and peroxisome proliferator-activated receptor gamma (PPARγ). SPHK2 phosphorylates the pro-drug FTY720 (fingolimod, which is used to treat some forms of multiple sclerosis) to a mimic of S1P and that acts as a functional antagonist of $S1P_1$ receptors. Inhibitors of SPHK1 and SPHK2 have therapeutic potential in many diseases.

Nomenclature	sphingosine kinase 1	sphingosine kinase 2
Common abbreviation	SPHK1	SPHK2
HGNC, UniProt	*SPHK1*, Q9NYA1	*SPHK2*, Q9NRA0
EC number	2.7.1.91: sphingosine + ATP = sphingosine 1-phosphate + ADP dihydrosphingosine + ATP = sphingosine 1-phosphate + ADP	2.7.1.91: sphingosine + ATP = sphingosine 1-phosphate + ADP dihydrosphingosine + ATP = sphingosine 1-phosphate + ADP
Cofactors	Mg^{2+} [536]	Mg^{2+}
Inhibitors	SKI II (pK_i 4.8) [181], MP-A08 (pIC_{50} 4.6) [474]	MP-A08 (pK_i 5.2) [474], SKI II (pK_i 5.1) [196]
Selective inhibitors	PF-543 (pK_i 8.4) [537]	SLC4101431 (pK_i 7.1) [100], compound 27d (pIC_{50} 6.8) [526], opaganib (pK_i 5) [181], ROMe (pK_i 4.8) [354]
Comments	SK1 inhibitors induce its proteasomal degradation [373, 404]. SK1 crystal structures confirm that it is dimeric [5]; there is no crystal structure available for SK2.	There is no crystal structure available for SK2.

Comments: MP-A08 is competitive with ATP; other SPHK inhibitors are competitive with sphingosine. ABC294640 (opaganib) has known off-target effects on dihydroceramide desaturase (*DEGS1*) [404, 610]) and induces proteasomal degradation of SK1 [404]. ABC294640 is in clinical trials for advanced cholangiocarcinoma, advanced hepatocellular carcinoma and refractory/relapsed multiple myeloma (to view ClinicalTrials.gov list click here).

Further reading on Sphingosine kinase

Adams DR *et al.* (2016) Sphingosine Kinases: Emerging Structure-Function Insights. *Trends Biochem. Sci.* **41**: 395-409 [PMID:27021309]

Lynch KR *et al.* (2016) Sphingosine kinase inhibitors: a review of patent literature (2006-2015). *Expert Opin Ther Pat* **26**: 1409-1416 [PMID:27539678]

Pitman MR *et al.* (2016) Recent advances in the development of sphingosine kinase inhibitors. *Cell. Signal.* **28**: 1349-63 [PMID:27297359]

Pulkoski-Gross MJ *et al.* (2018) An intrinsic lipid-binding interface controls sphingosine kinase 1 function. *J. Lipid Res.* **59**: 462-474 [PMID:29326159]

Pyne NJ *et al.* (2017) Sphingosine Kinase 2 in Autoimmune/Inflammatory Disease and the Development of Sphingosine Kinase 2 Inhibitors. *Trends Pharmacol. Sci.* **38**: 581-591 [PMID:28606480]

Pyne S *et al.* (2018) Sphingosine Kinases as Druggable Targets. *Handb Exp Pharmacol* [PMID:29460151]

Sphingosine 1-phosphate phosphatase

Enzymes → Sphingosine 1-phosphate turnover → Sphingosine 1-phosphate phosphatase

Nomenclature	sphingosine-1-phosphate phosphatase 1	sphingosine-1-phosphate phosphatase 2
Common abbreviation	SGPP1	SGPP2
HGNC, UniProt	*SGPP1*, Q9BX95	*SGPP2*, Q8IWX5
EC number	3.1.3.-: sphingosine 1-phosphate -> sphingosine + inorganic phosphate	3.1.3.-: sphingosine 1-phosphate -> sphingosine + inorganic phosphate
Comments	Depletion of S1P phosphohydrolase-1 (SPP1), which degrades intracellular S1P, induces the unfolded protein response and endoplasmic reticulum stress-induced autophagy [382].	–

Comments: SGPP1 and SGPP2 are non-redundant endoplasmic reticulum enzymes that dephosphorylate intracellular S1P. The phenotype of *Sgpp1*(-/-) mice differ with genetic background. *Sgpp2*(-/-) mice are also available. No specific SGPP inhibitors available [382].

Further reading on Sphingosine 1-phosphate phosphatase

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Huang WC *et al.* (2016) Sphingosine-1-phosphate phosphatase 2 promotes disruption of mucosal integrity, and contributes to ulcerative colitis in mice and humans. *FASEB J.* **30**: 2945-58 [PMID:27130484]

Lépine S *et al.* (2011) Sphingosine-1-phosphate phosphohydrolase-1 regulates ER stress-induced autophagy. *Cell Death Differ.* **18**: 350-61 [PMID:20798685]

Mandala SM *et al.* (2000) Molecular cloning and characterization of a lipid phosphohydrolase that degrades sphingosine-1- phosphate and induces cell death. *Proc. Natl. Acad. Sci. U.S.A.* **97**: 7859-64 [PMID:10859351]

Taguchi Y *et al.* (2016) Sphingosine-1-phosphate Phosphatase 2 Regulates Pancreatic Islet β-Cell Endoplasmic Reticulum Stress and Proliferation. *J. Biol. Chem.* **291**: 12029-38 [PMID:27059959]

Sphingosine 1-phosphate lyase

Enzymes → Sphingosine 1-phosphate turnover → Sphingosine 1-phosphate lyase

Nomenclature	sphingosine-1-phosphate lyase 1
HGNC, UniProt	*SGPL1*, O95470
EC number	4.1.2.27: sphingosine 1-phosphate -> phosphoethanolamine + hexadecenal dihydrosphingosine 1-phosphate -> phosphoethanolamine + hexadecanal
Cofactors	pyridoxal 5-phosphate
Inhibitors	compound 31 (pIC_{50} 6.7) [242, 366, 529, 635]

Comments: THI (2-Acetyl-5-tetrahydroxybutyl imidazole) inhibits the enzyme activity in intact cell preparations [528].
Recessive mutations in the S1P lyase (*SGPL1*) gene underlie a recently identified sphingolipidosis: SPL Insufficiency Syndrome (SPLIS) [103].
A Phase 2 clinical trial of LX3305 (LX2931) for rheumatoid arthritis has been completed (see NCT00903383).

Further reading on Sphingosine 1-phosphate lyase

Bamborschke D *et al.* (2018) A novel mutation in sphingosine-1-phosphate lyase causing congenital brain malformation. *Brain Dev.* **40**: 480-483 [PMID:29501407]
Choi YJ *et al.* (2019) Sphingosine phosphate lyase insufficiency syndrome (SPLIS): A novel inborn error of sphingolipid metabolism. *Adv Biol Regul* **71**: 128-140 [PMID:30274713]
Lovric S *et al.* (2017) Mutations in sphingosine-1-phosphate lyase cause nephrosis with ichthyosis and adrenal insufficiency. *J. Clin. Invest.* **127**: 912-928 [PMID:28165339]
Prasad R *et al.* (2017) Sphingosine-1-phosphate lyase mutations cause primary adrenal insufficiency and steroid-resistant nephrotic syndrome. *J. Clin. Invest.* **127**: 942-953 [PMID:28165343]

Thyroid hormone turnover

Enzymes → Thyroid hormone turnover

Overview:
The thyroid hormones triiodothyronine and thyroxine, usually abbreviated as triiodothyronine and T_4, respectively, are synthesized in the thyroid gland by sequential metabolism of tyrosine residues in the glycosylated homodimeric protein thyroglobulin (*TG*, P01266) under the influence of the haem-containing protein iodide peroxidase. Iodide peroxidase/TPO is a haem-containing enzyme, from the same structural family as eosinophil peroxidase (*EPX*, P11678), lactoperoxidase (LPO, P22079) and myeloperoxidase (MPO, P05164). Circulating thyroid hormone is bound to thyroxine-binding globulin (SERPINA7, P05543).

Tissue deiodinases
These are 1 TM selenoproteins that remove an iodine from T_4 (3,3′,5,5′-tetraiodothyronine) to generate triiodothyronine (3,3′,5-triiodothyronine, a more potent agonist at thyroid hormone receptors) or rT_3 (rT3, 3,3′,5′-triiodothyronine, a relatively inactive analogue). DIO1 is also able to deiodinate RT3 to form 3,3′-diidothyronine (T_2). Iodotyrosine deiodinase is a 1TM homodimeric enzyme.

Nomenclature	thyroid peroxidase	iodothyronine deiodinase 1	iodothyronine deiodinase 2	iodothyronine deiodinase 3	iodotyrosine deiodinase
Common abbreviation	TPO	DIO1	DIO2	DIO3	IYD
HGNC, UniProt	*TPO*, P07202	*DIO1*, P49895	*DIO2*, Q92813	*DIO3*, P55073	*IYD*, Q6PHW0
EC number	1.11.1.8: [Thyroglobulin]-L-tyrosine + H_2O_2 + H^+ + I^- -> [Thyroglobulin]-3,5,3'-triiodo-L-thyronine + [thyroglobulin]-aminoacrylate + H_2O	1.97.1.10: T_4 -> triiodothyronine rT_3 -> T_2	1.97.1.10: T_4 -> triiodothyronine rT_3 -> T_2	1.97.1.11: T_4 -> triiodothyronine rT_3 -> T_2	1.22.1.1: 3-iodotyrosine -> L-tyrosine + I^- 3,5-diiodo-L-tyrosine -> 3-iodotyrosine + I^-
Cofactors	Ca^{2+}	–	–	–	flavin adenine dinucleotide, NADPH
Inhibitors	methimazole [430], propylthiouracil [430]	–	–	–	–
Comments	Carbimazole is a pro-drug for methimazole	–	–	–	–

Further reading on Thyroid hormone turnover

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Gereben B *et al.* (2015) Scope and limitations of iodothyronine deiodinases in hypothyroidism. *Nat Rev Endocrinol* **11**: 642-652 [PMID:26416219]

Mondal S *et al.* (2017) Novel thyroid hormone analogues, enzyme inhibitors and mimetics, and their action. *Mol. Cell. Endocrinol.* **458**: 91-104 [PMID:28408161]

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van der Spek AH *et al.* (2017) Thyroid hormone metabolism in innate immune cells. *J. Endocrinol.* **232**: R67-R81 [PMID:27852725]

1.14.13.9 Kynurenine 3-monooxygenase

Enzymes → 1.14.13.9 Kynurenine 3-monooxygenase

Nomenclature	kynurenine 3-monooxygenase
HGNC, UniProt	*KMO*, O15229
EC number	1.14.13.9 L-kynurenine + NADPH + O_2 <=> 3-hydroxy-L-kynurenine + NADP(+) + H_2O
Comments	Kynurenine 3-monooxygenase participates in metabolism of the essential amino acid tryptophan.

Further reading on 1.14.13.9 Kynurenine 3-monooxygenase

Dounay AB *et al.* (2015) Challenges and Opportunities in the Discovery of New Therapeutics Targeting the Kynurenine Pathway. *J. Med. Chem.* **58**: 8762-82 [PMID:26207924]
Erhardt S *et al.* (2017) The kynurenine pathway in schizophrenia and bipolar disorder. *Neuropharmacology* **112**: 297-306 [PMID:27245499]
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Song P *et al.* (2017) Abnormal kynurenine pathway of tryptophan catabolism in cardiovascular diseases. *Cell. Mol. Life Sci.* **74**: 2899-2916 [PMID:28314892]

2.5.1.58 Protein farnesyltransferase

Enzymes → 2.5.1.58 Protein farnesyltransferase

Overview: Farnesyltransferase is a member of the prenyltransferases family which also includes geranylgeranyltransferase types I (EC 2.5.1.59) and II (EC 2.5.1.60) [82]. Protein farnesyltransferase catalyses the post-translational formation of a thioether linkage between the C-1 of an isoprenyl group and a cysteine residue fourth from the C-terminus of a protein (*ie* to the CaaX motif, where 'a' is an aliphatic amino acid and 'X' is usually serine, methionine, alanine or glutamine; leucine for EC 2.5.1.59) [188]. Farnesyltransferase is a dimer, composed of an alpha and beta subunit and requires Mg^{2+} and Zn^{2+} ions as cofactors. The active site is located between the subunits. Prenylation creates a hydrophobic domain on protein tails which acts as a membrane anchor.

Substrates of the prenyltransferases include Ras, Rho, Rab, other Ras-related small GTP-binding proteins, G-protein γ-subunits, nuclear lamins, centromeric proteins and many proteins involved in visual signal transduction.

In relation to the causative association between oncogenic Ras proteins and cancer, farnesyltransferase has become an important mechanistic drug discovery target.

Information on members of this family may be found in the online database.

Further reading on 2.5.1.58 Protein farnesyltransferase

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Shen M *et al.* (2015) Farnesyltransferase and geranylgeranyltransferase I: structures, mechanism, inhibitors and molecular modeling. *Drug Discov. Today* **20**: 267-76 [PMID:25450772]
Shen Y *et al.* (2015) The Recent Development of Farnesyltransferase Inhibitors as Anticancer and Antimalarial Agents. *Mini Rev Med Chem* **15**: 837-57 [PMID:25963569]
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3.5.1.- Histone deacetylases (HDACs)

Enzymes → 3.5.1.- Histone deacetylases (HDACs)

Overview: Histone deacetylases act as erasers of epigenetic acetylation marks on lysine residues in histones. Removal of the acetyl groups facilitates tighter packing of chromatin (heterochromatin formation) leading to transcriptional repression.
The histone deacetylase family has been classified in to five subfamilies based on phylogenetic comparison with yeast homologues:
Class I contains HDACs 1, 2, 3 and 8
Class IIa contains HDACs 4, 5, 7 and 9
Class IIb contains HDACs 6 and 10
Class III contains the sirtuins (SIRT1-7)
Class IV contains only HDAC11.
Classes I, II and IV use Zn^{+} as a co-factor, whereas catalysis by Class III enzymes requires NAD^{+} as a co-factor, and members of this subfamily have ADP-ribosylase activity in addition to protein deacetylase function [521].
HDACs have more general protein deacetylase activity, being able to deacetylate lysine residues in non-histone proteins [104] such as microtubules [270], the hsp90 chaperone [326] and the tumour suppressor p53 [377].
Dysregulated HDAC activity has been identified in cancer cells and tumour tissues [355, 509], making HDACs attractive molecular targets in the search for novel mechanisms to treat cancer [639]. Several small molecule HDAC inhibitors are already approved for clinical use: romidepsin, belinostat, vorinostat, panobinostat, belinostat, valproic acid and tucidinostat. HDACs and HDAC inhibitors currently in development as potential anti-cancer therapeutics are reviewed by Simó-Riudalbas and Esteller (2015) [545].

Nomenclature	histone deacetylase 6
HGNC, UniProt	*HDAC6*, Q9UBN7
EC number	3.5.1.98
Inhibitors	trichostatin A (pK_i 9) [61], vorinostat (pK_i 8.8) [61], romidepsin (pK_i 8) [61]
Selective inhibitors	ricolinostat (pIC_{50} 8.3) [518]

Further reading on 3.5.1.- Histone deacetylases (HDACs)

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Zagni C *et al.* (2017) The Search for Potent, Small-Molecule HDACIs in Cancer Treatment: A Decade After Vorinostat. *Med Res Rev* **37**: 1373-1428 [PMID:28181261]

3.5.3.15 Peptidyl arginine deiminases (PADI)

Enzymes → 3.5.3.15 Peptidyl arginine deiminases (PADI)

Overview: In humans, the peptidyl arginine deiminases (PADIs; HGNC family link) are a family of five enzymes, PADI1-4 and PADI6. PADIs catalyze the deimination of protein L-arginine residues to L-citrulline and ammonia, generating peptidyl-citrulline on histones, fibrinogen, and other biologically relevant proteins. The human isozymes exhibit tissue-specific expression patterns [294]. Overexpression and/or increased PADI activity is observed in several diseases, including rheumatoid arthritis, Alzheimer's disease, multiple sclerosis, lupus, Parkinson's disease, and cancer [47]. Pharmacological PADI inhibition reverses protein-hypercitrullination and disease in mouse models of multiple sclerosis [423].

Information on members of this family may be found in the online database.

Further reading on 3.5.3.15 Peptidyl arginine deiminases (PADI)

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Tu R *et al.* (2016) Peptidyl Arginine Deiminases and Neurodegenerative Diseases. *Curr. Med. Chem.* **23**: 104-14 [PMID:26577926]

Whiteley CG. (2014) Arginine metabolising enzymes as targets against Alzheimers' disease. *Neurochem. Int.* **67**: 23-31 [PMID:24508404]

3.6.5.2 Small monomeric GTPases

Enzymes → 3.6.5.2 Small monomeric GTPases

Overview: small G-proteins, are a family of hydrolase enzymes that can bind and hydrolyze guanosine triphosphate (GTP). They are a type of G-protein found in the cytosol that are homologous to the alpha subunit of heterotrimeric G-proteins, but unlike the alpha subunit of G proteins, a small GTPase can function independently as a hydrolase enzyme to bind to and hydrolyze a guanosine triphosphate (GTP) to form guanosine diphosphate (GDP). The best-known members are the Ras GTPases and hence they are sometimes called Ras subfamily GTPases.

RAS subfamily

Enzymes → 3.6.5.2 Small monomeric GTPases → RAS subfamily

Overview: The RAS proteins (HRAS, NRAS and KRAS) are small membrane-localised G protein-like molecules of 21 kd. They act as an on/off switch linking receptor and non-receptor tyrosine kinase activation to downstream cytoplasmic or nuclear events. Binding of GTP activates the switch, and hydrolysis of the GTP to GDP inactivates the switch.

The RAS proto-oncogenes are the most frequently mutated class of proteins in human cancers. Common mutations compromise the GTP-hydrolysing ability of the proteins causing constitutive activation [564], which leads to increased cell proliferation and decreased apoptosis [674]. Because of their importance in oncogenic transformation these proteins have become the targets of intense drug discovery effort [33].

Information on members of this family may be found in the online database.

Further reading on RAS subfamily

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Quah SY *et al.* (2016) Pharmacological modulation of oncogenic Ras by natural products and their derivatives: Renewed hope in the discovery of novel anti-Ras drugs. *Pharmacol. Ther.* **162**: 35-57 [PMID:27016467]

Simanshu DK *et al.* (2017) RAS Proteins and Their Regulators in Human Disease. *Cell* **170**: 17-33 [PMID:28666118]

RAB subfamily

Enzymes → 3.6.5.2 Small monomeric GTPases → RAB subfamily

Overview: The Rab family of proteins is a member of the Ras superfamily of monomeric G proteins. Rab GTPases regulate many steps of membrane traffic, including vesicle formation, vesicle movement along actin and tubulin networks, and membrane fusion. These processes make up the route through which cell surface proteins are trafficked from the Golgi to the plasma membrane and are recycled. Surface protein recycling returns proteins to the surface whose function involves carrying another protein or substance inside the cell, such as the transferrin receptor, or serves as a means of regulating the number of a certain type of protein molecules on the surface (see HGNC RAB, 65 genes).

Information on members of this family may be found in the online database.

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